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Adipose Tissue as a Site of Toxin Accumulation

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Abstract

We examine the role of adipose tissue, typically considered an energy storage site, as a potential site of toxicant accumulation. Although the production of most persistent organic pollutants (POPs) was banned years ago, these toxicants persist in the environment due to their resistance to biodegradation and widespread distribution in various environmental forms (e.g., vapor, sediment, water). As a result, human exposure to these toxicants is inevitable. Largely due to their lipophilicity, POPs bioaccumulate in adipose tissue, resulting in greater body burdens of these environmental toxicants with obesity. POPs of major concern include polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins and furans (PCDDs/PCDFs), and polybrominated biphenyls and diphenyl ethers (PBBs/PBDEs), among other organic compounds. In this review, we 1) highlight the physical characteristics of toxicants that enable them to partition into and remain stored in adipose tissue, 2) discuss the specific mechanisms of action by which these toxicants act to influence adipocyte function, and 3) review associations between POP exposures and the development of obesity and diabetes. An area of controversy relates to the relative potential beneficial versus hazardous health effects of toxicant sequestration in adipose tissue.

Introduction

As the name implies, POPs are organic lipophilic compounds that are resistant to environmental degradation, exhibit considerable stability, and persist in the environment. Due to their low water solubility, POPs can present as vapors in the atmosphere or strongly bind to particulate matter in sediments, where the sediment may serve as a reservoir, removing the POPs from circulation (18). If disturbed, however, the POPs may be released from the sediment and travel far from their origin before being re-deposited. One hallmark characteristic of POPs is their ability to move up the food chain and increase in concentration, or biomagnify, subsequently resulting in widespread environmental and human exposure (18). This is largely due to the high degrees of halogenation, which allows them to resist degradation by metabolizing enzymes. The bioaccumulation potential of these compounds can allow them to biomagnify to potentially dangerous levels (193) (245).

To address the global concern of environmental pollutants, 90 countries signed a United Nations treaty in 2001, known as the Stockholm Convention (18). The intention of the Convention was to severely limit, but preferentially eliminate, the widespread production and use of POPs. Recognizing the potentially toxic effects of POPs on human and environmental health, a preliminary list of chemicals known as the “dirty dozen” was established (18). This original list of 12 key POPs included aldrin, chlordane, dichlorodiphenyltrichloroethane (DDT), dieldrin, endrin, heptachlor, hexachlorobenzene,

mirex, toxaphene, polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (dioxins), and polychlorinated dibenzofurans (furans) (18). Since then, this list has expanded to include additional compounds, such as polycyclic aromatic hydrocarbons (PAHs), brominated flame retardants (BFRs), and other compounds that have proven particularly harmful and toxic to humans and animals (see Table 1 for a full list of abbreviations that will be used throughout the text). The primary route of human exposure to POPs is via food contamination, where fatty foods (e.g. meat, fish, and dairy) are important vectors for many classes of POPs, including PCBs, polybrominated flame retardants, dioxins and furans (PCDDs/PCDFs), and other organochlorines (Table 2).

When considering the toxicity of POPs, it is important to discuss their relationship with adipose tissue (AT), a significant site of toxicant bioaccumulation. AT is a connective tissue that is primarily comprised of white or brown adipocytes, but also contains several other cell types. White adipocytes are the most common type of fat cell, serving as a storage depot for lipids that are released upon need as an energy source. By comparison, brown adipocytes, which are much less prevalent in adults, are enriched with specialized mitochondria that mobilize lipid to produce heat for maintenance of body temperature (347). Of the two primary types of adipocytes, white adipocytes, with a large unilocular lipid droplet, are the prominent storage site of lipophilic POPs. It has been suggested that AT plays a major role in the storage and overall toxicokinetics of hydrophobic xenobiotic POPs (202) (203) (213). In addition, the physical properties that enable certain toxins/toxicants to partition into lipid are important in determining the extent of AT POP sequestration. The octanol:water partition coefficient, for example, offers insight into a toxicant's ability to partition between water and organic matter, and provides a clearer understanding of a toxicant's potential biological uptake, accumulation, and storage in AT (213).

The collection and storage of POPs in fatty tissue can have both positive and negative consequences. One beneficial aspect of POP sequestration in AT is that the toxicant concentration in blood is decreased, limiting POP availability to other cells and tissues where they may have hazardous effects (213). In this manner, POP sequestration in AT lipids appears protective against the harsh effects of lipophilic toxicants (24) (27) (137) (399) (154) (123). On the contrary, bioaccumulation of POPs in expanded AT of obese subjects results in a significantly increased body burden (213). The tonic release of these chemicals into the systemic circulation, especially during periods of weight loss (96) (105) (202) (240) (213) (283), can pose tremendous threats on overall human health (202) (154) (316) (38) (39) (231). We review data on accumulation of specific POPs in AT, their mechanism of action, and influence on diseases associated with dysregulation of AT function.

Physico-chemical properties and lipids influence AT POP bioaccumulation

The dynamics of contaminant accumulation in and release from AT depends on their physic-chemical properties. The partition coefficient has proven to be a major parameter governing the uptake of lipophilic toxicants into adipocytes. However, even within a toxicant class, structural determinants dictate physico-chemical properties that determine AT accumulation. For example, different PCB congeners can display distinct uptake and storage dynamics into adipocytes (54) (250) (249). One study compared the accumulation potential in AT of three

PCB congeners: PCB −28, −153, and −118 based on each of the congeners physico-chemical features. Results indicated that the dynamics of accumulation varied between the congeners due to molecular size, molecular volume, and lipophilicity (54). Specifically, the degree of halogenation, or number and position of chlorine substituents on the PCBs, influenced their uptake and accumulation in adipocytes. PCB-28 entered adipocytes more rapidly than the other two congeners likely due to its smaller molecular weight, size, and lipophilicity, while PCBs −153 and −118 remained trapped in the lipophilic cell membrane and diffused more slowly into the intracellular, hydrophobic cytoplasm of the adipocyte (54).

The lipophilicity of a compound depends on its chemical structure, where bigger, more complex and halogenated compounds are typically more lipophilic and resistant to biodegradation (206). As early as the 1900s, researchers tested for lipophilicity by studying the uptake of nonpolar compounds using organic solvents, like octanol, as a surrogate for the organic matter present in organisms (345). Although not identical, the extent of chemical uptake from the water into the organic phase is proportional to what is expected and observed in organisms (345). The octanol-water partition coefficient (K_{ow}) is defined by the following equation: K_{ow} = Coctanol/Cwater, where Coctanol is the molar concentration of the compound in the octanol phase, and Cwater is the molar concentration of the compound in the aqueous phase when the system is at equilibrium (345). The adipose-serum partition coefficient determines the extent to which a chemical may accumulate in adipose (319); it is a ratio of the concentration of a chemical in adipose to serum at equilibrium. Typically, the distribution of xenobiotics into AT is dependent on a number of pharmacokinetic factors including tissue volume and blood flow (232). The standard approach assumes that the tissue is “flow limited,” which means that the venous blood leaving the organ is at equilibrium with the “well-stirred” tissue compartment (232). While this approach has proven valid for the distribution of various xenobiotics into tissues and organs, there are a number of chemicals for which this flow limited model has proven invalid, including highly lipophilic POPs (421) (190) (208) (232). These chemicals, along with other organic compounds, act according to a “diffusion-limited” model, which states that diffusion limitation is proportional to the octanol-water partition coefficient (K_{ow}) of a chemical (232).

Ultimately, diffusion limitation increases as K_{ow} increases. In support of the studies by Oberg et al. (294) who simultaneously measured PCB concentrations in rat plasma and adipose tissue, Levitt (232) found that hexachlorobenzene (HCB), hexabromobenzene, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and tetrabrominated dinenzo-p-dioxin (TBDD) have a “similar increase in diffusion limitation with increasing K_{ow}.” Specifically, results of the study showed that the “apparent” rat adipose perfusion rate was smaller for a PCB (0.005kg/min/kg) with a log K_{ow} greater than 7, while significantly larger (0.2 kg/min/kg) for chemicals with log K_{ow} less than 5 (232). Collectively, these studies support the notion that at steady-state conditions, the log K_{ow}, a measure of lipophilicity, can help predict the likelihood of a chemical to diffuse and accumulate into AT and contribute to steady-state body burdens. Table 3 provides an overview of the structures and partition coefficients of numerous POPs.

Lipids are generally the primary components of any tissue that determine the movement, distribution, and sequestration of hydrophobic compounds, and play a vital role in toxicant accumulation in tissues (41). The bioaccumulation potential of a toxicant can vary among different lipid classes. For example, phospholipids exhibit moderate polarity, while triglycerides and free fatty acids display neutral polarity, which can influence their tendency to accumulate toxicants (1). Despite the large number of cell types in AT (i.e. preadipocytes, fibroblasts, macrophages, etc.), storage of POPs is believed to primarily occur in adipocytes (54) whose cytoplasm is composed mainly of triglyceride droplets (341). There are reports indicating that TCDD and DDT are transported out of the gut into the triglyceride component of chylomicrons, which are responsible for delivering lipids absorbed from the intestine to AT (416) (205). Another study demonstrated that the extent of PCB accumulation in different adipocyte models directly correlated to the amount of cellular triglycerides (54). However, due to the high cost of analyzing toxicants in different lipid components, toxicants are generally reported as a measure of total lipids in tissues (54).

It appears that the type of fat storage may also contribute to AT toxicant accumulation. There are two major areas where AT deposits: 1) visceral AT (vAT), which surrounds internal organs and is generally considered to contribute to obesity-related diseases (275) (196) (257), and 2) subcutaneous AT (scAT), located beneath the skin. These AT locations can display unique structural features and properties that may influence the kinetics of toxicants. Although one study found no significant difference in POP accumulation between visceral versus subcutaneous AT (256), several studies found that visceral AT contained higher POP concentrations than subcutaneous AT (316). In an obese population in Portugal, endrin and endosulfan I and II were detected in more visceral compared to subcutaneous AT samples (316). Moreover, the total concentration of POPs was significantly higher ($p<0.001$) in vAT (213.9 + 204.2 ng/g fat) versus scAT (155.1 + 147.4 ng/g fat) (316). Although a greater percentage of the population had detectable levels of endosulfans I and II and methoxychlor in their visceral compared to subcutaneous AT, higher concentrations of each toxicant were detected in subcutaneous AT (316). Similarly, average concentrations of aldrin and median concentrations of lindane were higher in subcutaneous than visceral AT (316).

It is worth noting that a possible explanation for the varying concentrations of POPs in different types of AT may depend on the individual exposed to the toxicant and toxicant exposure duration (434). Orban et al. (303) noted that the effect of age was also a significant factor for the detection of nine PCDDs/PCDFs in AT, while no significant differences were associated with sex or race.

Numerous toxicants have been detected in different AT samples from various populations (Table 4). In humans, two of the most predominant chlordane-related contaminants (trans-nonachlor and oxychlordane) were detected in breast milk and AT (50). In addition, levels of PAHs, including anthracene, pyrene, benzo[e]pyrene, benzo[k]fluoranthene, benzo[a]pyrene, and benzo[g,h,i]perylene, were detected in AT samples in the range of 11 to 2,700 ng/g tissue (293). PAH refers to a ubiquitous group of over 100 environmental POPs that are composed of multiple aromatic rings containing only carbon and hydrogen. Total concentrations of PAHs in AT from Korean women ranged from 15 to 361 ng/g lipid (277), and levels of dioxin-like PCBs ranged from 4.1 to 125 ng/g lipid in a Chinese population

(353). Mean levels of chlorobenzenes, including pentachlorobenzene (PeCB), in human milk and adipose tissue samples ranged from undetectable to 146 ng/g (178). Some of the highest levels of polybrominated diphenyl ethers (PBDEs) in AT were found in a New York population, with concentrations ranging from 17 to an astounding 9,630 ng/g lipid weight (183).

Blood levels of POPs (as shown in Table 4) are commonly used to assess point exposures (33) (279) (55) (363) (416) (309) (319). Hydrophobic toxicants in blood often bind to lipoproteins and proteins. Many PCBs and other organochlorine pesticides found in blood, for example, are associated with the protein fraction and all major lipoprotein compartments, including very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) (416). Aldrin and dieldrin bind to VLDL and LDL to distribute preferentially to fat, while chlordecone and mirex preferentially bind albumin and HDL (363), and pentachlorophenol (PCP) strongly binds to plasma proteins (55). Furthermore, Ljunggren et al. (243) found that POP concentrations in LDL/VLDL were more associated with cancer, while POPs in HDL were more associated with cardiovascular disease. Although most PCDD/PCDF congeners are found in lipoproteins of blood, liver, and fat tissues (319), the more highly chlorinated congeners (penta-through octa-substituted) do not partition between the lipoprotein and protein fractions of blood (309). In addition, less than 20% of dichlorodiphenyldichloroethylene (DDE) or DDT was distributed in erythrocytes, but greater than 40% of dieldrin was detected in these blood cells (279).

Measurements taken in whole blood, serum and/or plasma are minimally invasive, but may add difficulty in comparing toxicant concentrations between blood samples and other tissues. For example, Teixeira et al. (389) reported that plasma levels of aldrin did not reflect levels accumulated in tissues, and Archibeque-Engle et al. (30) found no correlation between levels of 15 of 17 compounds in breast AT compared to serum. Thus, preferential binding of some toxicants to lipoproteins and various other lipid compartments in serum and AT may contribute to reported variance of blood levels versus toxicant concentrations in other tissues (434).

When discussing toxicants in AT, it is important to define the process of bioaccumulation, which refers to the build-up of substances in the body because the substance is not readily metabolized and excreted. Many organic compounds not only resist environmental degradation, but may also bypass liver biotransformation enzymes and diffuse into AT. Highly lipid soluble POPs can disseminate through the food chain by collecting in body fat and biomagnifying, or increasing in concentration as they move from one organism to another. For example, the northern elephant seal is a “marine mammal predator” at the top of the food chain that contains massive concentrations of environmental contaminants that are primarily stored in AT (249) (99) (250) (318) (2). Measurements of bioaccumulation in fish and other aquatic organisms is often reported as the bioconcentration factor (BCF), which is defined as the extent to which a chemical concentration in an aquatic organism exceeds the chemical concentration in surrounding water (206). BCFs also correlate with octanol-water partition coefficients (345). Table 4 summarizes various bioaccumulation studies in aquatic organisms.

Once sequestered in adipose, toxicants are not released until lipolysis occurs, often through weight loss, diet, and exercise. It has been well documented that throughout episodes of fasting or weight loss, AT serves as a source of PCBs due to lipid mobilization (202) (250) (249). With lipolysis, PCBs and other toxicants are not only released into blood but they also concentrate into remaining AT (72) (202) (250) (249). Although no link has been established, one hypothesis for the "heterogeneous release of PCBs" from AT is that during lipolysis, fatty acids are differentially mobilized from AT and may influence the release of some PCBs versus others (98).

The release of PCBs and other toxicants into systemic circulation can potentially expose an individual to various known hazardous effects. Therefore, measuring chemical contaminants (and/or their metabolites) in adipose and blood samples can provide great insight into overall exposures and body burden, which can strengthen the ability to determine associations between chemical exposures and the development of adverse health effects.

Effects of POPs on AT function

While epidemiological studies indicate an association between systemic POP concentrations and metabolic diseases (228) (382) (386), mechanisms mediating impairment of metabolism by POPs remain unclear. In addition to the central role that AT plays in maintenance of metabolism and energy homeostasis through storage of excess fuels as fat (lipogenesis) and mobilization of fatty acids for use as fuel (lipolysis), adipocytes secrete a multitude of adipokines that contribute to metabolic regulation and inflammatory responses. In addition, a major role of AT is expansion in response to metabolic excess, which is achieved through both an increase in adipocyte size (hypertrophy) and increased differentiation of preadipocytes to mature adipocytes (adipocyte differentiation). Given the central role of AT in regulation of body weight and metabolism, POP-mediated disruption of AT function may contribute to the development of obesity and related metabolic diseases. A summary of the effects of POPs on AT function, organized by pollutant class, is presented in Table 5, and a summary of the major mechanisms by which POPs are purported to influence AT function is presented in Table 6.

Adipocyte differentiation

Mechanisms regulating fat accumulation have been a major focus of research given the increased prevalence of obesity and associated health risks. Several studies have characterized the effects of POPs on the differentiation of progenitor cells and/or preadipocytes to mature, lipid-laden adipocytes but findings have been contradictory. Findings are further complicated by use of a variety of models. For example, use of preadipocyte cell lines with restricted potential to differentiate into other cell types (e.g. 3T3-L1 cells) versus use of multi- or pluri-potent stem cells (mesenchymal stem cells or stromal-vascular cells) can influence the experimental outcome. The effects of TCDD and dioxin-like PCBs on adipocyte differentiation have been the most heavily studied. TCDD has consistently been shown to decrease adipocyte differentiation *in vitro* in 3T3-L1 cells (354) (161) and from stromal vascular cells (56). Further, TCDD (in an aryl hydrocarbon receptor (AhR)-dependent manner) was demonstrated to suppress hormone-induced

adipogenesis in mouse embryonic fibroblasts that exhibited proliferative expansion, but did not exit the cell cycle when exposed to the toxicant, suggesting that TCDD is an early regulator of adipocyte differentiation (26). However, effects appear to be dose-dependent. Low doses of both TCDD and dioxin-like PBC-77 induced differentiation of 3T3-L1 adipocytes, while high doses had an inhibitory effect (34). These results suggest that the reported effect of TCDD at high doses to induce wasting syndrome (348) may relate to an ability of the toxicant to decrease adipocyte differentiation, while lower exposures may contribute to an obesogenic phenotype. By comparison, studies examining effects of various organochlorine pesticides such as the non-dioxin-like PCB-153 (69), DDE (69) in human preadipocytes, and DDT in 3T3-L1 cells (278) report increased adipocyte differentiation. An ability of low dose POPs to induce adipocyte differentiation are consistent with increased body burden of these toxicants with obesity (332) (333) (104).

In addition to organochlorine pesticides, phthalates have also been associated with increased BMI and waist circumference (WC) in humans (370). Moreover, di(2-ethylhexyl) phthalate (DEHP) or its metabolite mono-(2-ethylhexyl) phthalate (MEHP) increased adipocyte differentiation in 3T3-L1 cells, (142) (115), murine mesenchymal stem cells (44), and *in vivo* (142) (62). Few human studies have addressed effects of BFRs on obesity and metabolic syndrome; however, adipocyte differentiation was increased by the BFRs PDBE (397) and BDE-47 (185). These findings are supported by a recent study which reported increased body weight of obese mice treated with hexabromocyclododecane (HBCD) (431). Other environmental toxicants (bisphenol A, BPA, bisphenol A diglycidyl ether, BADGE) have also been reported to increase adipocyte differentiation in 3T3-L1 cells (258), *in vivo*, (433) and in adipose stromal stem cells (297) (67).

Lipid Storage and Mobilization

Uptake of circulating fatty acids for storage as triglycerides is a major function of AT, with excess lipid accumulation a hallmark of expanded AT mass with obesity. In 3T3-L1 adipocytes, the organochlorine pesticides DDE, oxychlordane, and dieldrin have been reported to increase basal fatty acid uptake (160) and BPA was demonstrated to increase lipid accumulation (32). Administration of PCB-77 to mice resulted in greater body weight and adipocyte hypertrophy (34). Similarly, *in utero* exposure of mice to BPA (433) or the phthalates DHEP and MEHP increased adult fat mass, lipid accumulation and body weight (142) (373). However, in general, reports of direct effects of POPs to increase lipid accumulation are limited. As discussed below, and summarized in Table 6, it is likely that increases in lipogenesis or fat deposition can be attributed to impaired metabolism through endocrine disrupting effects of POPs.

In contrast, TCDD has been reported to reduce lipid accumulation and/or promote lipid mobilization (235) from adipocytes. This effect of TCDD has been attributed to inhibition of lipoprotein lipase (LPL), a key enzyme in the pathway for adipocyte uptake of fatty acids for storage as triglycerides (302) (195).

Adipokine secretion

A major function of AT is the secretion of a wide range of signals and factors termed adipokines. These include inflammatory cytokines (TNF-α, interleukins) and chemokines (MCP-1), as well as hormones that participate in body weight regulation and glucose and lipid homeostasis (adiponectin, leptin, resistin) (396). Reduced adiponectin levels (237) and increased resistin levels (177) with obesity are associated with insulin resistance and inflammation (237). Several studies have linked BPA exposure with regulation of AT adipokines. A study in obese children reported an association of urinary BPA concentration with insulin resistance, and incubation of AT explants from these patients with BPA increased gene expression of resistin and decreased gene expression of adiponectin (264). Similarly, incubation of adult AT explants with BPA inhibited adiponectin (166). In contrast, one study reported an increase in leptin and adiponectin expression in 3T3-L1 cells incubated with BPA (385). As BPA was also reported to increase adipocyte differentiation, it is possible that the increase in leptin and adiponectin reflected an increase in the mature adipocyte population. In addition to BPA (404) (32) (433), gene expression and secretion of inflammatory factors from adipocytes has been reported to increase in response to TCDD (195) (235) (34) (292) (203), PCB-77 (34) PCB-126 (203), and DEHP (62). Moreover, infiltration of macrophages into AT, a pathway associated with obesity-induced insulin resistance, has been reported as a result of exposure to DEHP (a phthalate) (62) HBCD (a BFR) (431), and TCDD (415).

Glucose uptake

Glucose uptake by adipocytes contributes to whole body glucose homeostasis and impaired glucose uptake is associated with insulin resistance. A vast majority of data indicate that POPs impair glucose uptake in adipocytes. Specifically, treatment of adipocytes with TCDD, PCBs, DDT, BFRs, BPA, and PAHs impaired glucose uptake. Exposure of animals to PCBs (38), phthalates (142) (374), BFRs (431), or mixtures of POPs (336) impaired insulin sensitivity. Mechanisms for these effects are not fully understood, but may include reduced AT levels of Glut-4 mRNA or increased expression of inflammatory markers (both AT and circulating levels) associated with impaired glucose uptake or insulin resistance.

Mechanisms of POPs to impair AT function

1. AhR—AhR is a basic-helix-loop-helix Per-ARNT-SIM (bHLH-PAS) ligand-activated transcription factor (136). Evolutionarily well-conserved, and expressed across a diverse number of mammalian species, AhR is a prominent mediator of the biological response to synthetic and naturally occurring chemicals (102). Ligand binding results in translocation of AhR from the cytoplasm to the nucleus and subsequent dimerization with its binding partner, aryl hydrocarbon receptor nuclear translocator (ARNT). The activated AhR/ARNT heterodimer complex binds to DNA at specific response elements (typically dioxin or xenobiotic response elements; DRE or XRE) to activate the expression of AhR target genes, such as cytochrome P450s (CYP1A1) (140). This classical activation of AhR has been described in response to halogenated aromatic hydrocarbons (HAHs), such as PCDDs, TCDD (being the best characterized and most potent), PCDFs, several PCBs, and PAHs (339).

AhR is expressed in adipocytes (354), and the adipocyte AhR has recently garnered increased attention for its role not only in the xenobiotic response of AT, but also as a regulator of body weight, fat mass, and lipid homeostasis (194) (39) (430). Several studies provide evidence of AhR-mediated regulation of AT function, but results have not been consistent. AhR activation was reported to suppress de novo lipogenesis, as mouse embryonic fibroblasts isolated from AhR deficient mice displayed enhanced triglyceride synthesis (26). These data are consistent with results from mice with adipocyte-specific deficiency in AhR, where mice displayed increased body weight, fat mass, AT inflammation, and decreased glucose tolerance compared to wild type mice when fed a high fat diet (39). In direct contrast, it was recently reported that high-fat fed mice with whole body deficiency of AhR were protected from obesity, insulin resistance, and adipose inflammation (430). In another study, aged, but not young mice with whole body AhR deficiency were reported to have impaired glucose tolerance compared to wild type controls, without concomitant differences in body weight between genotype (46). Differences in findings from mice with whole body AhR deficiency versus those with cell-specific deletions may result from diverging effects of AhR across multiple cell types. Taken together, data implicate AhR in the regulation of AT function, body weight and lipid homeostasis.

As a wide spectrum of ligands are capable of binding and activating AhR, its activation by various POPs may contribute to their observed effects on obesity and fat mass in human populations. The best characterized AhR agonists capable of eliciting effects in AT or adipocyte cell lines are TCDD and TCDD-like PCBs, which can be abolished by AhR antagonists (34) (121). Moreover, TCDD-induced impairment of adipogenesis in mouse embryonic fibroblasts was abolished when cells were isolated from AhR deficient mice (26). Further, effects of TCDD and TCDD-like PCBs to regulate the inflammatory response (204) (37) and glucose uptake in adipocytes (37) were AhR-mediated. In mice with whole body AhR deficiency, administration of PCB-77 resulted in adipocyte hypertrophy and increased body weight compared to wild-type mice (34). Moreover, effects of PCB-77 to impair glucose homeostasis and AT inflammation were abolished in mice with adipocyte-specific AhR deficiency (39).

PAHs are also high-affinity ligands for AhR (102). However, limited studies have defined effects of PAHs to regulate AT function and development of obesity. Exposure of mice to air pollution (a major source of PAHs) (377) or to benzo-[a]-pyrene (173) increased visceral AT, circulating inflammatory factors, AT macrophage infiltration, fat mass, body weight, and impaired whole body glucose tolerance (377). In humans, prenatal exposure to air pollution has been associated with increased body size in children (335) (260). Additionally, a consistent association exists between exposure to cigarette smoke (another PAH source) *in utero* and increased risk of overweight and or obesity in adulthood (300) (171). Whether PAH molecules impair AT function through AhR-mediated activation is unknown.

2. PPARγ—PPARγ, a ligand-activated nuclear transcription factor, is a central regulator of AT function. Specifically, the PPARγ2 isoform is predominantly expressed in adipose tissue, especially very early in adipose cell differentiation (365), and activation of PPARγ2 stimulates adipogenesis (393). Upon activation and formation of a heterodimer with the co-activator retinoid × receptor (RXR), PPARγ binds to PPARγ response elements to stimulate

transcription of genes involved in adipogenesis, lipid metabolism, and glucose homeostasis (22). It is thought that inappropriate activation of PPARγ by some POPs may contribute to obesity. In particular, phthalates have been identified as modulators of PPARγ. In 3T3-L1 adipocytes, activation of endogenous PPARγ target genes has been demonstrated by MEHP, monobenzyl phthalate (MBzP), and mono-sec-butyl phthalate (MBuP) (167). Moreover, direct activation of PPARγ by MEHP in 3T3-L1 adipocytes promoted adipocyte differentiation, albeit to a lesser extent than the known PPARγ agonist, rosiglitazone (115). Interestingly, compared to rosiglitazone, MEHP resulted in promotion of only a subset of PPARγ coregulators, indicating differential effects of MEHP versus rosiglitazone on PPARγ transcriptional activation of adipocyte gene expression (115).

Evidence suggests a link between AhR binding by POPs and PPARγ activation. Reduced differentiation of 3T3-L1 cells to adipocytes by TCDD (71) (161) (320), PCBs (121), or DDT (278) was associated with decreased PPARγ gene expression. Further, TCDD suppressed PPARγ and adipogenesis via a MEK/ERK mechanism (79). In contrast, in mouse embryonic fibroblasts, AhR-mediated inhibition of adipogenesis preceded suppression of PPARγ activity (26). Thus, changes in PPARγ expression in response to TCDD may reflect reduced adipocyte differentiation rather than a direct effect of AhR activation to decrease PPARγ.

One additional class of POPs that may influence PPARγ activity is organotins. Compounds such as tributyltin chloride (TBT) and bis(triphenyltin) oxide (TPTO) have been demonstrated to promote adipogenesis in 3T3-L1 cells through activation of PPARγ (186) (236). The effects of these compounds to influence PPARγ-mediated regulation of adipocyte function are thought to be through binding of the PPARγ binding partner, RXR (186) (221).

Although some BFRs have been associated with increased adipocyte differentiation, the mechanism has not been reported. The brominated analogs of BPA, TBBPA and TCBPA were demonstrated to bind to and activate PPARγ in reporter cell lines. It was observed that the bulkier the brominated BPA analogs, the greater their capacity to activate PPARγ (328).

3. Endocrine hormone receptors. Endocrine hormone receptors may be the target of many POPs. Endocrine disruption resulting from inappropriate interactions with these receptors can negatively influence obesity and AT function. Several POPs that accumulate in AT are reported to be xenoestrogens (environmental ligands capable of binding and influencing ER signaling) (334) (380) (220) (350), including BPA, DDT/DDE, methoxychlor, the PAH 2-amino-1-methyl-6-phenylimidazo[4–5-b]pyridine (PhIP), TCDD, PCBs, polybrominated biphenyls (PBBs), and phthalate esters. Estrogen receptor (ER) α and β are primary mediators of the effects of estrogens. Estrogen binding to these nuclear receptors results in the formation of homodimer complexes that bind to the promoter regions (termed estrogen response elements, or EREs) of estrogen-responsive genes, many of which contribute to regulation of metabolism. In post-menopausal women or ovariectomized rodents, where estrogen is low, white adipose tissue mass, body weight, and insulin resistance are increased (387). ERα signaling is purported to modulate the beneficial metabolic effects of estrogens, such as anti-lipogenesis, insulin sensitivity and glucose tolerance, and reduction of body weight and adipose mass, whereas ERβ is thought to play a larger role in the maintenance of normal glucose and lipid homeostasis (117). ERα deficient mice are prone to obesity,

exhibit increased visceral fat mass, decreased insulin sensitivity, and impaired glucose tolerance (149). ERs are expressed in AT (311) and adipocyte-specific deletion of ERα resulted in increased adiposity, AT inflammation and fibrosis (93).

In particular, BPA has garnered significant interest as an estrogenic compound. Despite having a relatively low affinity for the ER compared to that of estrogen (209), BPA is widely accepted to mimic the effects and potency of estrogen (410). However, BPA has been associated with increased adipocyte differentiation, body weight and fat mass, effects which are inconsistent with known ER-mediated reductions in adiposity as described above. A potential explanation for this discrepancy relates to a developmental window for the effects of BPA, as rodent studies have demonstrated a significant effect of prenatal BPA exposure to increase body weight, adipocyte hypertrophy, and adiposity in adults (410) (364) (272). In a recent study, BPA-mediated differentiation of human preadipocytes could be inhibited by an ERα antagonist (53). Estrogens contribute to an increase in adipocyte number (84). Thus, exposure to estrogen during a critical period of development may predispose for AT expansion, especially when children or adults are faced with a metabolic challenge, or in combination with exposure to other obesogenic environmental chemicals. The brominated BPA analogs TBBPA and TCBPA have also been described as ligands for ERs (329), but further mechanisms examining the role of these BFRs to modulate AT function through ERs have not been defined.

AhR has been reported to interact with endocrine hormone receptors, thus one mechanism by which AhR may mediate body weight and fat mass is through modulation of ER-signaling pathways. Ligand-bound AhR/ARNT has been demonstrated to directly associate with ERs (299); however, consequences of AhR/ER interaction are complex and not well understood. In general, crosstalk between ER and AhR is thought to be inhibitory with respect to ER signaling. An inhibitory effect of AhR on ER signaling is consistent with reports demonstrating AhR agonists increase body weight and adiposity, since deficiency of estrogen (387) or ERα (149) are associated with increased obesity and adipose mass.

Several mechanisms may contribute to inhibition of ER signaling as a result of ER/AhR crosstalk. First, TCDD-mediated expression of CYP1A1 and CYP1B1 has been reported to enhance metabolism of estrogen in some cell types (368) (366) (367). Although circulating estrogen levels were not altered in TCDD-treated rodents (355), no study has examined the relationship between AhR activation and adipose ER expression/activity. Moreover, ligand-bound AhR/ARNT prevents ER promoter binding and downregulation of ER target genes (reviewed in (340)). Also, ligand-bound AhR has been demonstrated to participate in an E3 ubiquitin ligase complex targeting the ER to proteasomal degradation (298). Finally, AhR and ERα interact with several common nuclear coregulatory factors (340), including ARNT (57), suggesting competition for these factors could influence activation of either pathway.

Inhibition versus potentiation of ER signaling may depend on the presence or absence of estrogen. For example, AhR coactivation of ERα resulted in transcriptional activity from ERE-regulated genes in the absence of estradiol (299). Alternatively, in the presence of estradiol, ARNT was recruited to estrogen-responsive promoters leading to increased ER transcription (379).

In addition to disruption of ER signaling, some lipophilic organochlorines may interfere with androgen receptor (AR) signaling. For example, DDT/DDE (191) and some PCBs (344) have been reported to act as AR antagonists. Testosterone has been shown to stimulate glucose uptake in adipocytes (271). Additionally, a positive correlation between insulin sensitivity and testosterone levels has been reported in males (321). Thus, antagonism of the AR by certain POPs may impair AT function through inhibition of glucose uptake.

AT is also a target of thyroid hormones, and thyroid hormone signaling through thyroid receptors (TRs) regulates lipid mobilization and storage. Disruption of TR signaling by certain POPs may contribute to dysregulation of AT function. For example, BPA has been reported to inhibit TR signaling through enhanced recruitment of corepressors (280); however, this effect of BPA has not been localized to AT. Exposure of rats to PDBEs resulted in increased circulating levels of thyroxine and altered glucose metabolism of isolated primary adipocytes, however there was no effect on body weight (155). Additionally, TCDD and certain PCBs have been suggested to be repressors of thyroid function, as exposed rodents (291) and humans (310) demonstrate compensatory increases in circulating levels of thyroid stimulating hormone. Future studies should address whether these TR-mediated effects are manifest in AT.

Associations between POP exposures and the development of obesity and diabetes

Obesity

The prevalence of obesity and its related comorbidities has been rising rapidly over the last three decades and is reaching epidemic proportions in the Western world, most notably in the US (244) (296). The rising prevalence of obesity becomes more alarming when considering that the comorbidities of overweight and obesity include an increased risk of type II diabetes and cardiovascular diseases (82) (273) (274), two leading causes of rising medical costs and poor prognosis in the US (266) (207). Interestingly, in parallel with the increased prevalence of obesity, the use and environmental levels of synthetic organic and inorganic chemicals has risen dramatically (35). Therefore, in addition to the importance of diet and exercise in the etiology of obesity (152), the hypothesis that exposure to environmental contaminants such as POPs contributes to the development of obesity is gaining popularity (35). The “obesogen hypothesis” proposes that exposure to environmental xenobiotic chemicals either *in utero* or throughout life contributes to the development of obesity (148) (109) (289). “Obesogens” have been defined as “molecules that inappropriately regulate lipid metabolism and adipogenesis to promote obesity” (135).

Previous reviews have investigated potential links between POPs and obesity (212) (228) (382); however, findings are often inconsistent between different POP classes and even within chemical congeners. Associations between POPs and obesity may be complicated by the lipophilicity of these compounds; obese individuals possess greater adiposity in which these lipophilic chemicals may be stored. Furthermore, obese individuals may consume more fatty foods rich in lipophilic chemicals and may, therefore, experience higher dietary exposure to POPs. Findings are further complicated by the dose and timing of exposure as

well as the gender of the individual exposed. Although *in vitro* and animal studies have typically investigated very high doses of POPs in their research, there is evidence that physiological changes can occur at much lower doses of POPs, and that these effects do not exhibit monotonic dose-response relationships (426). Therefore, conflicting findings between a particular POP and obesity may be explained by the level of exposure within the population. For example, toxic, high-dose exposures may result in weight loss while lower levels of exposure, which are characteristic of the typical population and may be considered "safe," might promote obesity (134) (148) (35). Additionally, the effects of POPs on parameters of obesity often vary by gender (Tables 7 and 8), which may be due to the POP's ability to disrupt endocrine function and mimic estrogenic effects (51). Lastly, the time of exposure poses an important consideration for investigating associations between POPs and obesity. Many POPs, including PCBs, DDE and HCB have shown contrasting effects on body mass index (BMI) in prenatal versus adult exposures (212). As such, associations between POPs and obesity will be investigated separately based on the timing of exposure: prenatal and early life, or adult exposure. Regardless of these interactions and individual effects of the chemicals, the net result of POP mixtures appears to be weight gain.

Prenatal and Early Exposure to POPs

Amidst the growing prevalence of obesity, rampantly rising rates of childhood obesity has emerged as a critical public health concern. Prevalence of childhood obesity worldwide has risen sharply since the 1980s, reaching 42 million in 2013 with estimates that this number will increase to 70 million infants and children in 2025 (305). The heightened concern over the childhood obesity crisis stems from both short-term and long-term effects on health and longevity. In the short term, obese children possess a higher risk for cardiovascular disease (120) and prediabetes (234). However, and perhaps even more frightening, is the association between childhood obesity and future risk of obesity (255) (36) (139), cardiovascular disease, type II diabetes, and greater morbidity and mortality (255) (36) (139) (285) (369). Together, these findings support the hypothesis of the fetal origins of adult disease, which proposes that the environment of the fetus can determine health and disease outcomes later in life (360).

Therefore, in accordance with the obesogen hypothesis, prenatal and early life exposure represents a critical window during which children are particularly vulnerable to both the short-term and long-term effects of POPs on obesity (134) (325) (290) (192). Furthermore, prenatal and early life contexts represent particularly vulnerable periods for environmental exposures. The fetus is sensitive to chemical exposures, which can cross the fetal-maternal blood barrier (175). This increased susceptibility continues into early life, as children have different levels and sources of exposure. Children can experience the effects of maternal exposure to POPs even after birth, as chemicals appear in breastmilk and represent a source of exposure during breastfeeding (31). Furthermore, children are not simply "tiny adults"; they differ not only in size but also in metabolism and physiological function, such as higher caloric consumption consumed per kg body weight and higher minute ventilation (361) (74), which can put them at increased risk of exposure to environmental chemicals. We describe below evidence regarding exposures to specific POPs and the development of obesity and/or diabetes.

1. PCBs and Dioxins—The effect of prenatal PCBs on obesity is inconclusive. Twelve of the 25 studies investigating prenatal PCBs found no association between prenatal and early exposure to PCBs and obesity (Table 7). However, of the 12 studies that did find an association between prenatal PCBs and obesity, 9 found that PCBs had an inverse association on measures of obesity, including birth weight (131, 151, 284, 308), growth rate (308), weight (174) (47) (176) (214), and BMI (104). Conversely, 5 studies found positive associations between prenatal and early PCB exposure and measures of obesity (104) (414) (383) (21) (408).

A factor that may complicate interpretation of these studies is differing effects of TCDD-like PCBs and non-TCDD-like PCBs, as well as different effects in males versus females. Two studies found differing effects between toxicants based on their similarity to TCDD within the same study population. In a study of early exposure in Flemish adolescents aged 14–15 years, serum TCDD-like PCBs were positively associated with increased BMI while non-TCDD-like PCBs were negatively associated with BMI in males and females (104). In a second study, which investigated prenatal PCBs and obesity in African American children of the National Collaborative Perinatal Project (NCPP), maternal levels of TCDD-like PCBs were negatively associated with girl's weight and marginally positively associated with boy's weight (214). Conversely, maternal levels of non-TCDD-like PCBs were not associated with weight (214). This study highlights a complexity in the relationship between prenatal PCBs and obesity: gender. Of the 14 studies that found some association between prenatal or early exposure to PCBs and obesity in study populations containing both males and females, 5 studies found different effects between males and females. For example, negative associations between PCB exposure and weight were reported in males with no effect in females (151) (174). Conversely, a positive association was reported between PCB exposures and obesity in females but not males (383) (408). Therefore, diverging effects of prenatal and early PCB exposure and obesity in males versus females may contribute to differences in findings between studies. In summary, study findings should consider gender of the population under study, as well as the type (e.g., TCDD-like) and/or individual congeners which are screened.

2. DDE and DDT—Fifteen of 24 studies that investigated DDE exposures found positive associations between prenatal and early exposure to DDE and measures of obesity including BMI (189) (402) (414) (265) (189) (95) (423), weight (174) (189) (127), overweight (21, 408), rapid growth (265) (407), and waist circumference (383, 402) (101, 423). Only one 4-year study on Russian boys aged 6–8 years found a negative association between DDE and BMI (58). Similar to PCBs and TCDD, there appear to be different effects between genders, as some studies found associations with obesity in females but not in males(95) (101) (408). Conversely, two studies found effects on BMI, waist circumference, and overweight and obesity at 9 years (423) and weight at 14 years (127) in males but not in females. Additionally, an association between prenatal DDE and BMI z-score and rapid growth that was seen in both sexes was stronger in boys (265). Therefore, the evidence supporting a link between prenatal DDE exposure and obesity is compelling despite potentially different effects between genders. By comparison, the effect of prenatal DDE on birth weight is less conclusive. One study showed an association between prenatal DDE and birth weight (248)

while another showed no association with birth weight (131). Therefore, while there is a strong argument for exposure to prenatal DDE and obesity in later life, the effects of DDE on birth weight are inconclusive and might be weakly associated with decreased birth weight.

Five studies investigating prenatal exposure to DDT and obesity outcomes were analyzed. Two studies in childhood and adolescent males found no association between prenatal DDT exposure and BMI in boys (126) (423). However, another study in 6.5-year-old children found a positive association between prenatal DDT and overweight in males but not in females (408). In a study of 7.5-year-old children of both genders, a nonsignificant association was found between maternal DDT and BMI and increased odds of overweight and obesity (422). Lastly, prenatal DDT was associated with decreased birth weight (248). Therefore, prenatal exposure to DDT may decrease birth weight while being weakly associated with overweight in childhood, particularly among boys.

3. Hexachlorobenzene (HCB), β-Hexachlorocyclohexane (HCH), and OC pesticides—Of the 11 studies which investigated the role of prenatal or early exposure to HCB and obesity, 5 found positive associations with HCB exposure and obesity. Four of the 5 studies found association between prenatal and maternal exposure to HCB and parameters of obesity including BMI (402) (362) (21), rapid growth (405) (407), and increased overweight and obesity (362) (21) (407). One study investigating early exposure to HCB and obesity found that in 7 year olds, HCB exposure was associated with increased BMI and overweight. However, a study investigating early exposure to HCB in 8–22 year olds found no association between HCB exposure and obesity (384). Furthermore, there were 4 studies that found no association between prenatal HCB and BMI (265) (90), obesity (90), birth weight (248), or waist circumference (101). One study found that exposure to HCB in 14–15 year olds decreased BMI. Studies appear to support an association between prenatal HCB exposure and rapid growth and increased BMI and overweight, particularly in childhood. However, the relationship between HCB exposure and obesity in adolescents is inconclusive.

Three studies investigating the effect of prenatal exposure to HCH failed to support an association between HCH and BMI (265) (90), obesity (90), or birth weight (248). However, conflicting associations were found when studying early exposure to HCH and obesity. There was an inverse association between β-HCH exposure and BMI in Russian boys aged 8–9 over a 4-year study (58). Conversely, Spanish children of both genders exhibited positive associations between β-HCH and BMI and increased overweight at 7 years (21). These conflicting findings might be due to gender, as boys exhibit a negative association between β-HCH and obesity while a positive association was seen when children of both sexes were studied, of which 51.3% were female. Furthermore, the two populations might differ in dose, type, or duration of exposure, as the two studies differed in which chemicals were included in their screening in addition to β-HCH.

A study investigating OC pesticides found no association between prenatal trans-nonachlor and oxychlordane and obesity or BMI at 7 years (90). However, the same study did find a positive association between prenatal dieldrin exposure and obesity but no association with BMI.

4. Polybrominated flame retardants (BFRs)—As compared to the organochlorines, fewer studies have investigated the prenatal or early exposure effects of BFRs on obesity, and the results are inconsistent. Of the 5 studies analyzed for the effects of BFRs, two found positive associations while two studies found negative associations between BFRs and obesity. A study in pregnant Long-Evans hooded rats found that prenatal dosing with PBDE-99 increased rat offspring birth weight (238). Furthermore, studies in humans have found the prenatal PBB exposure (above 5 ppb) was associated with increased weight for height in females (47). Conversely, studies in Mexican-Americans from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) found negative associations between maternal PBDE levels and BMI, waist circumference, and birth weight (113) (144). However, the association seen between PBDE and lower birth weight became nonsignificant when maternal weight gain was included in the analysis (144).

5. Polycyclic Aromatic Hydrocarbons (PAHs)—Maternal and early exposure to PAHs appears to have contrasting effects on birth weight and childhood obesity. Several studies have shown that maternal dietary (215) (180) and airborne PAH (215) exposure as well as PAH-DNA adduct levels in newborns (314) (315) are associated with reduced birth weight. Conversely, prenatal and early exposure to PAHs is positively associated with increased BMI, obesity, and waist circumference in childhood (197) (335) (346). Therefore, it appears that prenatal exposure to PAHs may reduce birth weight but increase the risk of childhood obesity.

6. Phthalate Esters—The findings of the relationship between prenatal and early exposure to phthalates and obesity is inconsistent and complicated by different effects between the two sexes and also between low molecular weight (LMW) and high molecular weight (HMW) phthalate metabolites. LMW metabolites, including MnBP, MEP, and MiBP, have been associated with childhood obesity (77) (145) (388) (59) (48). Conversely, HMW metabolites have been associated with lower weight gain and lower BMI z-scores in boys but higher BMI in girls (406).

7. Bisphenol A (BPA)—The effects of BPA seem to vary depending if the exposure was prenatal or early in life. Prenatal exposure to BPA has been shown to be negatively associated with BMI, adiposity, and percent body fat in young girls (403) (143) as well as associated with decreased birth weight (269). On the other hand, early exposure to BPA in ages 4–15 has been associated with increased BMI, obesity, and waist circumference (403) (143) (405) (417) (394); however, one study did show a negative association between BPA levels and BMI in 6–9 year old girls (428). Therefore, prenatal exposure to BPA seems to decrease the risk of obesity later in life while postnatal early exposure in childhood seems to increase the risk of childhood obesity.

Adult Exposure to POPs

In addition to the growing burden of obesity in children, more than 1.9 billion adults (39%) age 18 years and older were overweight in 2014, of which over 600 million (13%) were obese (306). Because adults experience a longer duration and type of exposure to POPs, they are presented separately from prenatal exposure. Furthermore, because maternal levels of

POPs can determine offspring health, adult women of the childbearing age are of particular interest in terms of obesity outcomes.

1. PCBs and Dioxins—The studies of PCBs and dioxins and obesity are, by far, the most complex of the POPs. Complications when studying PCBs and potential effects on obesity arise from different effects between congeners and genders and non-linear and inverted U-shaped associations. While dioxins have consistently shown positive associations with BMI (224), waist circumference (223), fat mass (332), and metabolic syndrome (399), PCBs have shown positive, negative, or null associations between studies. These consistencies appear to be due to different effects between congeners and between genders.

TCDD-like PCBs have been positively associated with BMI (312) (128) (104). However, the non-TCDD-like PCBs have produced more inconsistent associations. For example, non-TCDD-like PCBs have been both negatively (224) (106) (104) (128) and positively (312) (223) associated with BMI and waist circumference. Furthermore, less-chlorinated PCBs have been positively associated with weight gain (241) and fat mass, while highly-chlorinated PCBs have been negatively associated with weight gain (241) and fat mass . Furthermore, several studies have reported conflicting associations with PCBs and obesity within the same study that varied by congener (226) (332). When PCBs were grouped together, positive associations were found with an increased risk of becoming obese (108), BMI (218), and waist circumference (223). Furthermore, in a study of obese adults without diabetes, adipose levels of PCBs were positively associated with weight, BMI, waist circumference, and visceral adipose tissue (107).

Additionally, studies have found different effects of PCBs between genders. In the PIVUS study by Lee et al. on older adults, women had positive associations between waist circumference and the PCB congeners 74, 99, 118, 138, 153, and 156, but negative associations with congeners 105 and 126 (226). Similar inconsistencies in waist circumference were present in men, with PCBs 156, 157, 169, 180, 189, and 209 positively associated and PCBs 74, 99, 106, 118, 126, 138, 153, 170, 194, and 206 negatively associated with waist circumference. As discussed previously, study results must be considered with attention to the specific congeners studied and the gender of the study population. Lastly, the effects of PCBs also vary by dose, with several studies reporting nonmonotonic and inverted U-shaped associations (226) (230) (96) (333) (223), indicating that lower doses of PCBs might produce greater effects on obesity development than higher doses.

2. DDE and DDT—Of the fourteen studies that measured DDE in regards to obesity outcomes, thirteen found positive associations and only one study found no association. Therefore, DDE has consistently been positively associated with BMI (230) (224) (107) (104) (218) (128) (164) (312) (343), waist circumference (223) (107) (226), and visceral and subcutaneous adipose tissue (107). Only two studies found sex differences in the relationship between DDE exposure and obesity. In a study of the NHANES 1999-2002 data set, DDE was positively associated with waist circumference in women but negatively associated in men (110). On the other hand, in the PIVUS study of older adults, Lee et al. found that DDE was associated with waist circumference in males but not in females (226). Therefore, the

literature supports a positive association between DDE and obesity, although gender differences may exist.

Fewer studies have investigated a relationship between DDT and obesity. In the Coronary Artery Risk Development in Young Adults (CARDIA), a prospective study in young adults without diabetes, DDT positively predicted BMI (230). On the other hand, in a cross-sectional study on Canadian males, DDT was not associated with BMI (312). However, these inconsistent results may be a result of gender differences, as a cross-sectional study on the 1999–2002 NHANES dataset found that DDT was positively associated with waist circumference in females, but negatively associated in males (110).

3. HCB, β-HCH, and OC pesticides—The effects of HCB, β-HCH, and the remaining organochlorine pesticides, such as oxychlordane, trans-nonachlor, mirex, and aldrin, are less clear than the strongly positive associations of DDE with obesity. However, the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study in older adults found that the sum of OC pesticides was positively associated with weight gain (241). Of these pesticides, studies on HCB and β-HCH tend to support positive associations with obesity. HCB has been positively associated with BMI (104) (218) (128) (312), waist circumference (226) and fat mass (332) (230). Similarly, β-HCH has been positively associated with BMI (312) (106, 164), metabolic syndrome (391), waist circumference (106), and fat mass (106). The Chlordane constituents oxychlordane and trans-nonachlor have been positively associated with BMI (164), waist circumference (226), and visceral and subcutaneous adipose tissue (96). However, several studies have also shown no association between chlordane and measures of obesity (230) (224) (164). The other OC pesticides have not been studied as extensively; however, three studies have reported no association between mirex and BMI (230) (164) (312). On the other hand, aldrin has been positively associated with metabolic syndrome (MetS) (391).

4. BFRs—Two studies have investigated PBBs and PBDEs levels in adults, and both supported positive associations between BFR exposure and obesity. In a study of the 2003-2004 NHANES data set, PBB-153 was nonlinearly associated with MetS and WC; furthermore, PBDE-153 exhibited an inverted U-shaped association with MetS (239). These results indicate that potential associations between BFRs and obesity in adults may be complicated by nonmonotonic dose response curves. Additionally, a second study in pregnant women found that milk levels of PBDEs were associated with the mom’s BMI (91). Therefore, not only were PBDE levels associated with maternal BMI, but these levels in milk also represent a source of early life exposure to BFRs in offspring, which represents a potential factor in health outcomes later in life.

5. PAHs—One study investigated urinary PAH metabolites and obesity; however, the results were inconsistent and varied between metabolites (324). While urinary 2-phenanthrene was positively associated with obesity, 1-naphthalene was negatively associated with obesity in NHANES adults (324). Additionally, 2-naphthalene, 1-phenanthrene and 2-phenanthrene were positively associated with MetS. Furthermore, studies on smoking cigarettes, which can be a source of exposure to PAHs, have found positive associations with central obesity (75).

6. Phthalate Esters—As in prenatal exposure, the relationship between phthalates and adult obesity is complicated by gender, age, and differences between the groups of phthalate metabolites; however, studies generally support a positive association between phthalate exposure and adult obesity. In a study of the 1999–2002 NHANES data set, although females had higher urinary levels of phthalate metabolites, the strongest positive associations with BMI and WC were found in 20–59-year old males with MBzP, MEHHP, and MEOHP (145). For LMW metabolites, MEP was positively associated with BMI in adult males (20–59 and 60–80 years old) and for adolescent and adult (20–59 years old) females; however, no association was found in adolescent males and an inverse relationship was found in older females (145). Furthermore, while MBP showed inverse trends with BMI and WC in 60–80 year olds and female adults (20–59 years old), positive trends existed in 20–59-year old males (145). Furthermore, while the high molecular weight metabolite MBzP had a positive association with BMI and WC of 20–59-year old males, no associations were seen in females (145). Of urinary DEHP metabolites, MEHP was inversely associated with BMI and WC in adolescent and adult females, but no associations were found in males. On the other hand, MEHHP was positively associated with BMI in males, but no associations were found in females (145). Again, apparent inconsistencies between studies on phthalates and obesity might be explained by the particular metabolites studied and the age and gender of study participants.

7. BPA—Few studies have investigated relationships between BPA and obesity. Three studies support positive associations between BPA exposure and abdominal obesity (65) (420) as well as WC (122).

Diabetes

The global prevalence of diabetes is staggering; the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014, corresponding to an increase from 4.7% to 8.5% of adults over 18 years of age (304). Type 1 diabetes (T1D) is an autoimmune disease characterized by insulin deficiency as a result of beta-cell failure. On the other hand, Type 2 diabetes (T2D) is characterized by insulin resistance and includes an alarming number of children and adolescents (424).

There has been a growing interest in the environmental contribution to the etiology of diabetes and obesity. In 2011, the US National Toxicology Program (NTP) and the National Institute of Environmental Health Sciences (NIEHS) conducted a workshop titled “Role of Environmental Chemicals in the Development of Diabetes and Obesity” to investigate the science studying POPs and their association to these two diseases. The workshop concluded that there is a strong argument for a role of POPs in the etiology of diabetes and obesity (390) (386). The importance of studying the influence of environmental pollutants on the development of these diseases has been acknowledged by the National Institutes of Health (NIH) (146), the National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) (83) (24), and the White House Task Force on Childhood Obesity (40).

The ubiquitous exposure to low and chronic levels of POPs presents a complicating factor in linking these toxicants to diabetes, as there is no true reference population with zero

exposure to POPs. Moreover, the majority of studies that have attempted to link POP exposures to diabetes have focused on background levels within the general population, as opposed to occupational exposures. Background level POP exposures within the general population are present as mixtures of chemicals. Therefore, findings from studies investigating individual POPS must be analyzed in reference to not only the other POPs studied, but also the total mixture of chemicals to which the population is exposed. Two prospective studies have investigated the effect of POPs as mixtures on diabetes incidence, and both studies found that exposure to POP mixtures is associated with a 3–5 time higher risk of developing T2D (227) (229). In the Coronary Artery Risk Development in Young Adults (CARDIA) study, an inverted U-shaped association between exposure to POP mixtures and diabetes was found in young adults (229). The inverted U-shaped association indicates a nonmonotonic dose-response relationship between POPs and diabetes. Similarly, in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, an association between POP exposure and T2D in the elderly was found (227). However, while this association suggested nonlinearity (227), it was not a clear inverted U-shaped association as in the CARDIA study.

1. PCBs and Dioxins—High-dose, toxic levels of chemical exposure have been the focus of both animal and human studies to investigate associations between exposures and effects on human health. For example, early findings on the human effects of TCDD were studied in populations with occupational and accidental exposure, such as U.S. Air Force veterans exposed to Agent Orange in Vietnam (150) (200) (187) and workers and residents exposed to TCDD following accidents or spills at chemical plants (43) (437) (371). Unfortunately, these early findings were inconsistent, as positive (150) (200) (187), inverse (371) (437), and null associations (381) (413) were observed between TCDD and T2D.

The findings from the Air Force Study on Vietnam War veterans of Operation Ranch Hand exposed to Agent Orange highlight the perplexing relationship between POPs and T2D. Compared to those not exposed to TCDD-contaminated Agent Orange, US Air Force veterans exposed to Agent Orange had glucose abnormalities and a higher risk of T2D (150). However, a follow-up study excluded veterans exposed to Agent Orange and only considered veterans who did not come into contact with TCDD-contaminated herbicides and, therefore, had exposure levels consistent with background levels in the United States (247). In this second study, the dose-response relationships between TCDD and T2D were surprisingly stronger in veterans with background levels of exposure as compared to high occupational exposure to TCDD, indicating that not only do POPs have low level effects on T2D, but also that these associations might be unexpectedly stronger at lower, background exposure levels (247).

This puzzling association between lower doses of TCDD and T2D was reinforced by a study of occupational exposure following a chemical plant accident in Italy (43). Of residents living in high-, medium, and low-exposure areas surrounding the accident, there was higher T2D mortality in the medium-exposure area as compared to residents from the high-exposure area (43). Furthermore, in occupational exposure studies on individuals with very high levels of TCDD exposure, no associations were found between TCDD exposure and T2D (61) (381) (437). In contrast, recent studies in heavily contaminated areas, such as

Superfund sites, demonstrate associations between serum TCDD and PCB levels and T2D (357) (411) (401), as well as elevated glucose (218) (86). While it remains debatable whether direct associations exist between exposure levels and T2D, reports demonstrating that lower level POP exposures are associated with diabetes are alarming, as these levels can be found in most individuals, and certainly in the obese population. A summary of POPs and their links to T2D are presented in Table 9.

2. DDE and DDT—In adults with both background and occupational exposure, DDE and DDT have been linked with diabetes and related phenotypes. For adults with higher than background exposure levels to environmental contaminants, two studies investigating a heavily polluted area of Eastern Slovakia found associations between DDE and DDT and diabetes (218) (401). In one study, DDE and DDT were associated with both prediabetes and diabetes in these heavily exposed Slovakian adults (401). In a second study in this Slovakian population, DDE correlated with fasting glucose and serum insulin (218). Furthermore, DDE was also found to have a positive association with diabetes prevalence in women in the Anniston Superfund site (357). In studies in adults with background levels of exposure to POPs, DDE has been associated with T2D prevalence (224) (80) (398) (24) (337) (85), glucose abnormalities (107), and HOMA-IR (230). Additionally, studies have found associations between DDT and diabetes (114) (85).

Of particular interest are two studies performed in obese adults with background exposure who underwent bariatric surgery, which allowed for the researchers to obtain fat depots and evaluate associations between adipose levels of DDE and diabetes (107) (316). Both serum and adipose levels of DDE were associated with glucose levels and an abnormal glucose tolerance test (GTT) (107). In a second study by Pestana et al., (316), not only were total POPs in adipose tissue associated with HOMA-IR and dysglycemia, but adipose levels of DDE were associated with glucose metabolism and HbA1c. Similar findings across studies, as well as associations between both serum and AT levels to diabetes, support potential contributions of DDE exposures to the development of diabetes.

3. HCB, HCH, and OC pesticides—HCB, HCH, and the OC pesticides, such as oxychlordane, heptachlor, trans-nonachlor, and aldrin, have consistently shown positive associations with diabetes. When grouped together as OC pesticides, studies have found associations with high fasting glucose (223), diabetes prevalence (225), and incident T2D (227). When investigated individually, studies of these pesticides have largely indicated positive associations between exposure levels and diabetes. HCH has been associated with prediabetes (401), diabetes (85), and elevated serum glucose (85), while HCB was associated with diabetes prevalence (80) (337) and incidence (429). Chlordane and its constituents and metabolites heptachlor, trans-nonachlor, and oxychlordane have found positive associations with diabetes. Of the chlordane constituents, trans-nonachlor and oxychlordane have been the most heavily studied. These constituents have been positively associated with T2D prevalence (224) (85) (24), diabetes incidence (227) (229), and HOMA-IR (222). In contrast, while low doses of mirex were found to be associated with diabetes incidence in young adults of the Coronary Artery Risk Development in Young Adults (CARDIA) study (229), mirex was negatively associated with diabetes in adults of

the Mohawk Nation at Akwesasne (80). Despite these inconsistent findings for mirex, which might be due to differences in study population and outcomes (diabetes prevalence versus diabetes incidence), OC pesticides appear to be consistently associated with diabetes.

4. BFRs—Literature on polybrominated flame retardants and diabetes are inconsistent, with studies showing either positive or no associations. Two main categories of BFRs have been investigated-PBDEs and PBBs. Studies on PBDEs have produced inconsistent findings in relationship to obesity, which may represent differing effects between PBDE congeners. In NHANES 2003-2004, PBDE-153 showed positive associations with diabetes prevalence and glycemia (239). In the same study, PBDE-99, PBDE-100, PBDE-28, and PBDE-47 were not significantly associated with diabetes. However, in a study of a cohort of sport fish consumers, the sum of PBDEs and the PBDE congeners PBDE-47 and PBDE-153 were not associated with diabetes (398). As described previously for other POP classes, individual congeners of PBDE may have some association with obesity and/or diabetes, but generalizations from mixed exposures cannot be assumed.

The findings for PBBs are similarly inconsistent. While PBB-153 was found to be positively associated with prevalent diabetes and glycemia in adults within NHANES 2003–2004 (239), prospective studies on PBB exposures and diabetes incidence have been inconsistent in their findings. In the CARDIA prospective study, low doses of PBB-153 were found to be associated with an increased risk of diabetes incidence (229); however, a prospective study of a Michigan cohort found no association between PBB and diabetes incidence (411).

5. PAHs—Although PAHs have not been as extensively studied as other environmental contaminants for their potential relationship to diabetes, the studies reviewed here show positive associations between PAH exposure and diabetes. In studies of merged 2001–2006 NHANES data, urinary PAH biomarkers, 1-naphthalene, 2-naphthalene, 2-phenanthrene, and 1-pyrene were associated with diabetes in adults (28) (324). Furthermore, in a study of Chinese adults, urinary PAH metabolites had a dose-response association with an increased risk of diabetes (432). Therefore, although the literature for PAH exposure and diabetes is not as extensive as other POPs, results support an association between PAHs and diabetes prevalence.

6. Phthalate Esters—While studies have often found positive associations between phthalates and diabetes, there are inconsistent findings that may be attributable to differing effects between phthalate metabolites, categorized as DEHP metabolites, low molecular weight metabolites, or high molecular weight metabolites. Urinary DEHP metabolites (MEHP, MECPP, MEHHP, MEOHP) have been positively associated with diabetes (378), HOMA-IR (395) (163), insulin resistance (395), and fasting levels of blood glucose and insulin (163). However, studies on LMW metabolites (MEP, MBP, MiBP, and MBP) have yielded inconsistent results. In an analysis on the Nurses' Health Study (NHS) and NHSII female adults, MBP, MiBP, and total phthalate metabolites were positively associated with incident T2D in the younger NHSII cohort; however, no association was found between phthalates and incident T2D in the older NHS cohort (376). In data from NHANES 2001–2008 in adults without diabetes, MnBP and MiBP were positively associated with fasting blood levels of glucose and insulin and HOMA-IR (163). Furthermore, adult males in

NHANES 1999–2002 had positive associations between MEP and HOMA (370). In contrast, results from studies in adults outside of NHANES have failed to show associations between LMW metabolites and diabetes. In NHANES adolescents and elderly Korean adults, no associations were found between LMW phthalates and HOMA-IR (201) (395). The high molecular weight metabolites (MBzP, MCPP) have yielded perhaps the most inconsistent results. While MECPP positively associated with fasting blood levels of glucose and insulin and HOMA-IR (163), MBzP has been both positively and negatively associated with diabetes. In 1999–2002 NHANES, MBzP was associated with increased HOMA in adult males (370). However, in a study of healthy Mexican women, MBzP was negatively associated with diabetes (378). Therefore, the effect of phthalates on diabetes may differ depending on the particular metabolite examined, but also depending on the gender of the exposed individual. **7. BPA.** Results from studies examining BPA exposures have generally supported a positive association between both serum and urine BPA and diabetes incidence (376), diabetes prevalence (20) (23) (349) (216), HbA1c (23), and impaired fasting glucose (20). However, two studies found no association between BPA and diabetes (201) (376). Differences in the relationship between BPA and diabetes between these studies could potentially be explained by the age of the population or the amount or duration of exposure.

In summary, in general, evidence supports an association between POPs, obesity and diabetes, particularly among the extensively-studied organochlorines. The relationship between POPs and obesity and diabetes may be complicated by differing effects between individual congeners, between genders, and between ages. Age may add complexity to the study of the role of environmental pollutants on diabetes due to the two phases of diabetes pathogenesis: insulin resistance and beta cell dysfunction. The age at the time of study and the age of diabetes onset may determine the relative importance of each phase of pathogenesis, as age is associated with greater beta cell dysfunction and insulin secretory effects (68). The stage of diabetes pathogenesis of the individuals within a study may, therefore, result in distinctive overall associations with POPs and dose-response relationships. Furthermore, an interaction of age on the association between adiposity and diabetes risk has been suggested (45), which deserves particular attention considering the complexity that obesity adds to the study of diabetes.

The consistent findings of nonmonotonic and inverted U-shaped associations between POPs (particularly PCBs) and disease outcomes are of particular interest. As compared to a linear dose response, in which the sign of the slope (i.e. negative or positive) does not change, a nonmonotonic relationship is characterized by a dose response curve with a slope that changes sign over the range of concentrations studied. These nonmonotonic dose response relationships indicate that lower levels of POPs, such as those in background levels of the general population, may be more harmful in terms of the development of diabetes and obesity than high exposures experienced in chemical spills. An inverted U-shaped association indicates that the maximal effect (i.e. highest disease incidence or prevalence) is observed at intermediate concentrations of POPs and drops off at increasing doses. Inverted U-shaped associations could explain the seemingly conflicting results of studies investigating the effects of POPs on obesity and diabetes. Different studies may indeed investigate different portions of the U-shaped curve based on the range of exposure

concentrations studied. For example, studies in a population with low exposures may observe the initial positive linear portion of the inverted U, while studies in populations with intermediate and high exposure concentrations could experience null or inverse associations. Furthermore, studies are complicated by the lack of a true reference population, as all individuals are exposed to some level of POPs. Therefore, low, chronic exposure to POPs may be more detrimental to health than previously thought. The effects at background levels of exposure may not be properly predicted by studies performed in populations with high, occupational exposure in POPs exhibiting nonmonotonic dose responses.

Potential mechanisms to explain the inverted U-shaped associations observed in studies of the effect of exposure to POPs on obesity and diabetes may stem from the effects these toxicants have as endocrine-disrupting chemicals, including cytotoxicity, cell-specific receptors, differences in receptor selectivity, receptor downregulation, desensitization, and receptor competition (409). Cytotoxicity, perhaps the simplest explanation for nonmonotonic responses, could explain how disease prevalence is increased at low concentrations, at which the toxicant can exert physiological effects, but disease prevalence drops off at higher concentrations at which the POP becomes acutely toxic (409). Furthermore, dose response to POPs is complicated by cell-specific receptors that can activate different pathways. Different receptors may have different responses to a POP, and a single cell might exhibit different responses at different concentrations of exposure; as such, these overlapping responses can create an nomonotonic association overall (409). Furthermore, a response to a particular POP may decrease at increasing concentrations due to receptor downregulation, degradation, and desensitization (409). Therefore, an inverted U-shape curve may result from a decreased number of receptors or a decreased receptor response at increasing concentrations of POPs. An additional factor that may contribute to nonmontonic associations between exposure levels and disease is the ability of some POPs to induce enzymes involved in their own metabolism and detoxification. Lastly, nonmonotonic responses can occur due to receptor competition, which may be particularly relevant given that exposure, particularly background levels of exposure, to POPs occurs as a mixture and not as a single toxicant.

Obesity contributes to the development of diabetes; furthermore, as previously discussed, increased consumption of fatty foods can increase the body burden of lipophilic POPs, and expanded adipose tissue in obesity serves as a reservoir of POPs. Just as obesity and weight loss can alter the balance between sequestration in fat and release of POPs into the bloodstream, diabetes development and progression may influence the circulating levels of POPs, which raises issues of potential reverse causality. Just as circulating POP levels are dictated not only by exposure, but also by the individual’s history of weight gain and loss, serum levels of POPs at the time of study may be influenced by the progression of diabetes, complicating any potential associations. Simply put, are higher serum levels of POPs contributing to the development and progression of diabetes or is diabetes pathogenesis altering the metabolism of POPs, leading to an increase in serum levels? These are important considerations to be made when analyzing the existing literature and when formulating new studies on POPs and health outcomes.

Conclusion

It is clear that POPs have physical characteristics that enable their bioaccumulation in adipose tissue, resulting in greater body burdens of a wide array of environmental toxicants with distinct mechanisms of action in the setting of expanded AT mass. It is also clear that accumulating evidence supports a role for various POPs in the development of obesity, and in obesity-associated conditions such as type 2 diabetes. Association of POPs with obesity and/or diabetes have indicated that low level exposures, as would be experienced by the majority of US citizens, may influence not only the development of diabetes in adults, but also exert gestational influences that influence the health of offspring. There are many unanswered questions that warrant further investigation. Below, we summarize several unresolved issues and questions of significance related to POPs, AT, and disease development.

Do POPs contribute to the development of obesity and diabetes?

In 2013, at a National Toxicology Program Workshop, an evaluation of the literature in terms of consistency, strengths and weaknesses of the clinical diagnosis, exposure assessment and study population characteristics was performed to evaluate the area of POP exposures and diabetes outcomes (382). While the authors found that there was insufficient evidence to conclude a positive association of some organochlorine POPs with type 2 diabetes, strongest positive correlations occurred for DDE, PCBs, TCDD and TCDD-like chemicals. Within the appendix of this analysis, the authors provide an extensive list of data gaps and research recommendations that if performed, would provide more definitive information related to POP exposures and type 2 diabetes. It is unclear if any of these issues have been resolved to move this field forward.

Is bioaccumulation of POPs in AT helpful or harmful?

The physical chemical properties of POPs result in their bioaccumulation within adipocyte lipids. When trapped in triacylglycerol lipid droplets, POPs are sequestered away from target effectors, suggesting that bioaccumulation in adipocyte lipids may minimize harmful effects of POPs. However, sequestered POPs dynamically equilibrate between adipocyte lipids and the intracellular/extracellular environment, most likely resulting in low level tonic stimulation of effectors. Moreover, given that the total body burdens of lipophilic POPs increase with their bioaccumulation in an expanded AT mass of obese subjects, and that many POPs exert inflammatory actions that could contribute to the development of insulin resistance, low level POP exposures may contribute to the development of diabetes and other inflammatory-related conditions. Alternatively, when lipids are mobilized from adipocyte stores, POPs also mobilize and can act at effector targets to negatively influence health. As an example, given that 66% of the adult population are overweight and/or obese and attempting to lose weight, lipolysis-mediated release of POPs may negatively influence AT (and other target organs), mitigating the positive health benefits of weight loss. Therefore, areas of additional investigation would be identification of therapies and/or approaches that mitigate the harmful effects of liberated POPs. Moreover, it would be informative to understand ramifications of rapid versus slow weight loss as a means of influencing the bioaccumulation, actions and elimination of POPs from the body.

What are the implications of mixtures of POPs and their influence on AT function?

Our body burden of POPs reflects mixtures we are exposed to through the environment. As discussed, mechanisms of POPs to influence AT function vary, and this is complicated by not only differences in mechanism of action between parent compounds within mixtures, but also influences of metabolic bi-products of POP metabolism. Moreover, even within a given class of POPs, interactions with target effectors may occur through the same binding site, or through allosteric mechanisms, suggesting additive and/or synergistic effects of POP mixtures at a given target effector. An advantage of experimental models is that they enable investigators to determine effects of individual POPs at exposure levels that hopefully mimic those experienced by humans. However, humans are exposed to and bioaccumulate a broad array of POPs that are further influenced by not only the level of adiposity, but also influenced by the regional deposition of AT. Thus, further studies are needed to define molecular interactions of mixtures at specific target effectors, integrated whole body responses to POP mixtures, and the influence of regional AT deposition on bioaccumulation and health-related effects of POPs.

Is biomedical remediation of POPs possible?

Considerable efforts are underway to remediate POPs from our environment. In contrast, aside from reducing environmental exposures, there are few avenues available to remediate POP burdens from humans experiencing chronic low level exposures, or to treat acutely exposed populations. This is alarming, as obesity prevalence continues to increase in children and adults, resulting in greater body burdens of POPs. Moreover, a preponderance of evidence suggests that prenatal POP exposures negatively influence the health of offspring, and an alarming number of child-bearing women are overweight and/or obese and would predictably have increased body burdens of POPs during gestation. Thus, biomedical remediation is needed not only to influence the health of the mother, but to minimize potential harmful effects of POPs on future generations. Additional studies should identify potential therapies, including lifestyle interventions and/or pharmacologic approaches, that can mitigate the harmful effects of liberated or tonically released POPs that decrease the bioaccumulation of POPs in AT lipids, or that hasten their elimination.

Are there variables that influence the bioaccumulation within and/or toxicity of POPs at AT?

Results from human exposure studies suggest that dose-response relationships (e.g., nonmonotonic dose-response), gender, and POP chemical class influence their bioaccumulation in AT, effector mechanisms, and toxicity. However, mechanisms for these relationships are not well defined. For example, it is unclear why some studies indicate more prevalent associations between POP exposures and obesity/diabetes in females compared to males, or vice versa. Additional studies are warranted at the experimental level to dissect potential mechanisms for these variables and their influence on POP toxicity.

In conclusion, physical/chemical characteristics of lipophilic POPs result in their bioaccumulation in AT, a site where these toxicants not only are sequestered away from effector targets, but also where they may exert actions that influence metabolism. Given that almost all humans harbor some level of POPs, further studies are warranted to define their

contribution to diseases of increasing prevalence (obesity, diabetes), mechanisms of action, effects of POP mixtures, and the development of biomedical remediation therapies.

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Table 1

List of Abbreviations

AhR	Aryl hydrocarbon receptor
AR	Androgen receptor
ARNT	Aryl hydrocarbon receptor nuclear translocator
AT	Adipose tissue
BADGE	Bisphenol A diglycidyl ether
BCF	Bioconcentration factor
BDE	Brominated diphenyl ether
BFDGE	Bisphenol F diglycidyl ether
BFRs	Brominated flame retardants
β-HCH	β-Hexachlorocyclohexane
BMI	Body mass index
BP	Blood pressure
BPA	Bisphenol A
ClBPA	Monochloro-BPA
Cl_2BPA	Dichloro-BPA
Cl_3BPA	Trichloro-BPA
CYP	Cytochrome P450
DBP	Dibutyl phthalate
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DEHP	Di(2-ethylhexyl) phthalate
DRE	Dioxin response element
ER	Estrogen receptor
ERE	Estrogen response element
ERK	Extracellular signal-regulated kinase
Glut-4	Glucose transporter type 4
HAHs	Halogenated aromatic hydrocarbons
HBCD	Hexabromocyclododecane
HCB	Hexachlorobenzene
HDL	High density lipoprotein
HMW	High molecular weight
HOMA	Homeostatic model assessment
HOMA-B	Homeostatic model assessment-beta
HOMA-IR	Homeostatic model assessment- insulin resistance
HpCDD	1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin
HxCDD	1,2,3,4,7,8-Hexachlorodibenzo-p-dioxin
K_{ow}	Octanol-water partition coefficient

LDL	Low density lipoprotein
LMW	Low molecular weight
MEK	Mitogen-activated protein kinase kinase
MBP	Mono-butyl phthalate
MBuP	Mono-sec-butyl phthalate
MBzP	Monobenzyl phthalate
MCP-1	Monocyte Chemoattractant Protein-1
MEHHP	Mono(2-ethyl-5-hydroxyhexyl) phthalate
MEHP	Mono-(2-ethylhexyl) phthalate
MEOHP	Mono(2-ethyl-5-oxohexyl) phthalate
MEP	Mono-ethyl phthalate
MetS	Metabolic syndrome
MiBP	Mono-isobutyl phthalate
MnBP,	Mono-n-butyl phthalate
NDL	Non-dioxin-like
NHANES	National Health and Nutrition Examination Survey
OC	Organochlorine
OCDD	Octachlorodibenzodioxin
PAHs	Polycyclic aromatic hydrocarbons
PBBs	Polybrominated biphenyls
PBDEs	Polybrominated diphenyl ethers
PCBs	Polychlorinated biphenyls
PCDDs	Polychlorinated dibenzo-p-dioxins
PCDFs	Polychlorinated dibenzofurans
PCP	Pentachlorophenol
PeCB	Pentachlorobenzene
PhIP	2-amino-1-methyl-6-phenylimidazo[4-5-b]pyridine
POPs	Persistent organic pollutants
PPARγ	Peroxisome proliferator-activated receptor gamma
RXR	Retinoid X receptor
scAT	Subcutaneous adipose tissue
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TBBPA	Tetrabromobisphenol A
TBDD	Tetrabrominated dinenzo-p-dioxin
TBT	Tributyltin chloride
TCBPA	Tetrachlorobisphenol A
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TNF-α	Tumor necrosis factor alpha
TPTO	Bis(triphenyltin) oxide

TR	Thyroid receptor
vAT	Visceral adipose tissue
VLDL	Very low density lipoprotein
WC	Waist circumference
XRE	Xenobiotic response element

Table 2

General Characteristics of Toxicants

Category	Environmental Chemicals	Exposure	Use	General Characteristics
Polychlorinated biphenyls	PCBs	Air, Food	Industrial chemicals; By-products during combustion	**PCBs** consist of a family of 209 congeners (49), whose toxicity and persistence in the environment often increases with higher degrees of chlorination (half-lives can vary from months to years). PCBs have been banned in the U.S. since the 1970s, but are still evident in environmental and human samples (14). Prior to the ban, PCBs were used in a variety of industrial processes and were also produced as by-products during combustion (14).
Polychlorinated dibenzo-p-dioxins/Polychlorinated dibenzofurans	PCDDs/PCDFs	Air, Water, Food	Produced only for research purposes; By- products during combustion and other industrial processes	**PCDDs** are chemicals produced as by-products during the manufacture of pesticides and other chlorinated substances, like pentachlorophenol (PCP). There are about 75 different dioxins, 7 of which have ignited much concern, including TCDD (313). Like PCDDs, **PCDFs** are also produced unintentionally and have structural similarities to dioxins. As a result, they share many of the same toxic effects. However, there are about 135 different types of furans and their toxicities vary (313). Dioxins and furans can both exist in the environment for several years and can bioaccumulate in fatty tissue and biomagnify through the food chain (5). Furans are also classified as possible carcinogens.
Organochlorines	Aldrin/Dieldrin/Endrin	Soil, Air and Water	Insecticide	**Aldrin** and **dieldrin** were used as crop insecticides from 1950-1970 until banned by the Department of Agriculture, but were reintroduced by the EPA and used from 1972-1987 (3). Once aldrin enters the body, it is converted to dieldrin, and both can undergo degradation. **Endrin** is a chlorinated cyclodiene that was used as an insecticide and pesticide to control rodents and birds until its use was discontinued in the US in 1986. Endrin is a stereoisomer of dieldrin. Although similar in structure to other organochlorines, endrin is rapidly metabolized and does not accumulate in adipose to the same extent as other pesticides with similar structures.
	Chlordane/Heptachlor	Soil, Air and Water	Insecticide	**Chlordane** is an organochlorine mixture of over 140 different compounds with its main constituents being cis- and trans-chlordane, cis- and trans-nonachlor, and heptachlor (97). Trans-nonachlor and oxychlordane, the major metabolite of chlordane, are primary contaminants detected in human fat samples (50). Chlordane was used from 1948 -1979 when concerns of toxicity began to emerge. Use of chlordane in the 1980s was largely as an insecticide against termites until the sale and use of chlordane were halted in 1988 (4). However, the half-life for chlordane in soil is 10-20 years; therefore, this pesticide remained in soil surrounding areas treated with chlordane (42). **Heptachlor** is a component and degradation product of chlordane (10). It was used extensively prior to 1970, but now the only permitted use is for fire ant control. Heptachlor is converted to its epoxide, heptachlor epoxide, upon environmental exposure and human ingestion. The epoxide accumulates and biomagnifies in the food chain (10).
	Mirex/Chlordecone	Soil, Air and Water	Insecticide	**Mirex** is a derivative of cyclopentadiene, and was used in the United States in the 1960s and 1970s as a pesticide against fire ants and also as a flame retardant additive (13). **Chlordecone** is a transformation product of mirex. It was in use until 1977, but due to its stability, high lipophilicity, and resistance to metabolism it has a high potential to biomagnify in the food chain (111) (165). However, no information on level in humans or adipose is available.
	Methoxychlor	Soil, Air and Water	Insecticide	**Methoxychlor** was used as a pesticide from 1946 - 2000; it tightly binds to soil and exhibits estrogenic activity (12) (88).
	Endosulfan	Soil, Air and Water	Insecticide	**Endosulfan** was used as a pesticide since 1954, however following the 2011 Stockholm Convention, endosulfan use was completely discontinued by July 31, 2016 (8). Endosulfan is a derivative of hexachlorocyclopentadiene, and is chemically similar to aldrin, chlordane, and heptachlor. Technical-grade endosulfan is comprised of a 7:3 mixture of α- and β-endosulfan isomers, which are also known as endosulfan I and II, respectively (8). The β isomer slowly converts to the more stable α-endosulfan.
	Toxaphene	Soil, Air and Water	Insecticide	**Toxaphene**, a product of chlorine gas and camphene, is a pesticide that was used heavily in the southern US to control pests on livestock and crops. Although it was once one of the most heavily used pesticides, it has since been banned for use in the United States (15) (228).
	Hexachlorobenzene	Soil, Air and Water	Fungicide; Industrial Chemicals; By- products during combustion and other industrial processes; Impurities in certain pesticides	**Hexachlorobenzene** was introduced in 1945 as a fungicide to protect food crops. Due to its structural stability and resistance to biodegradation and metabolism, HCB is recognized as one of the most environmental persistent pollutants (11). The estimated half-life in soil is 3 - 6 years (11), and it can exist in the atmosphere and environment long after it is used. Hexachlorobenzene has also been used as a reference compound for BCFs in fish (19).
	p,p′-DDT/p,p′-DDE	Soil, Air, Water, and Food	Insecticide	**Dichlorodiphenyltrichloroethane (p,p′-DDT)** was initially used as an insecticide during WWI to protect against malaria, typhus, and other diseases transmitted by insects (6). It is an extremely persistent pollutant, with approximately 50% remaining in the soil 10-15 years after application. Although it was banned due to its toxic effects on birds, DDT has been detected in food worldwide. As such, food- borne DDT is the greatest source of human exposure. **p,p′- Dichlorodiphenyldichloroethylen e (p,p′-DDE)** is the primary metabolite produced by the dehydrochlorination of DDT in humans, and is also considered a persistent environmental pollutant that can have adverse effects on human health (33).
Polybrominated bi-/di- phenyl ethers	PBDEs/TBBPA/HBCD	Soil, Air, Food and	Flame retardants; Industrial chemicals; By -products of debromination of other BDEs	While brominated flame retardants are beneficial in numerous materials for their fire-resistant characteristics, some may pose a threat to human and environmental health. Since most flame retardants are not chemically bound to the material, they can leech into the environment, where they resist biodegradation. Of all the brominated flame retardants, PBDE, TBBPA, and HBCD rank highest in global consumption (138). **Polybrominated diphenyl ethers (PBDEs)** are generally characterized by two brominated biphenyl rings joined by an ether. All PBDEs are lipophilic substances that are very likely to adsorb on particulate matter and not likely to volatilize from water phase. **Tetrabromobisphenol A (TBBPA)** reactive flame is a retardant used in electric equipment. Although it is a polybrominated compound, it does not share the same toxicity profile as PBDEs. It is produced by brominating bisphenol A, and is rapidly metabolized after exposure (331) (359). TBBPA is not considered a persistent and bioaccumulative toxicant (63). TBBPA has a log K_{ow} of 6.53 at a low pH, but at pH 6-9 TBBPA is in a dissociated form and has a lower log K_{ow} (211). PBDEs, **hexabromocyclododecane (HBCD)**, and, to a lesser extent, TBBPA, are brominated biphenyl ethers that possess fire-resistant and degradation-resistant properties that allow them to bioaccumulate and move up the food chain (242) (281) (92). Note that HBCD is a brominated cyclic aliphatic compound, not a diphenyl ether.
Endocrine Disruptors	Phenols/Phthalates	Food, Water	Industrial chemicals	**Bisphenol A (BPA)** is most commonly used for “binding, plasticizing, or hardening plastics” and as an additive in flame retardants (116). Although BPA is not as persistent as other POPs, due to its common use, BPA is frequently released into the environment, which can lead to indirect human exposure. Phthalates are a class of compounds that are used for a variety of purposes and are generally non-persistent in humans (262) (156). **Di (2-ethylhexyl) phthalate (DEHP**) is a manufactured chemical that is commonly added to plastics to

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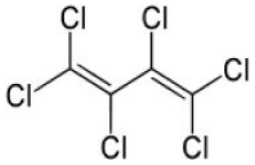
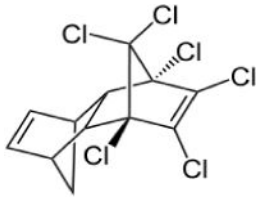
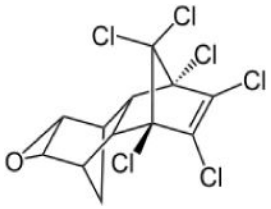
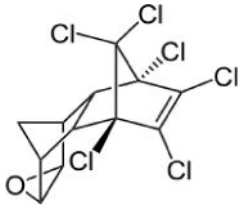
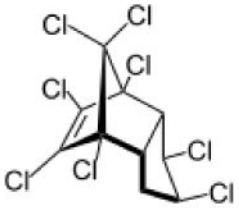
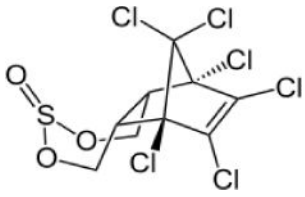
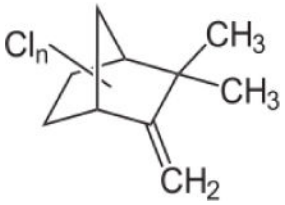
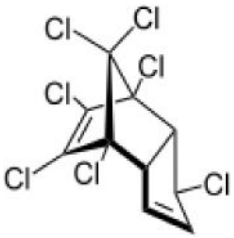
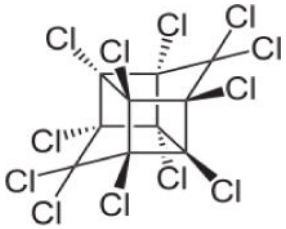
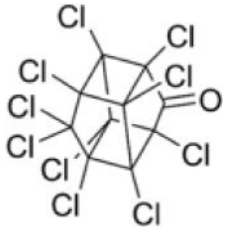
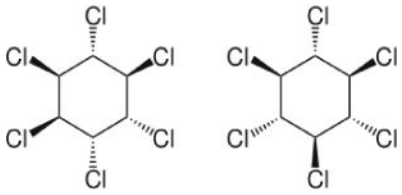
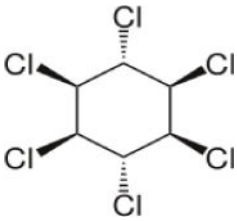
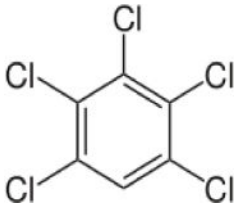
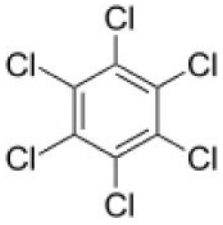
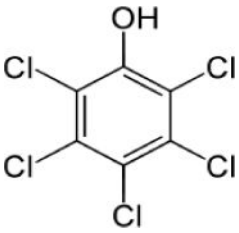
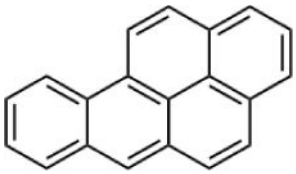
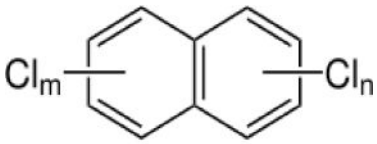
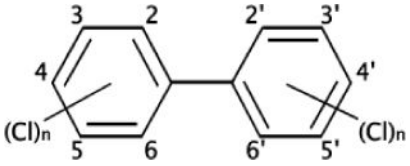
Category	Environmental Chemicals	Exposure	Use	General Characteristics
				increase their flexibility (7), and can be absorbed from food and water (351). **Mono-(2-ethylhexyl) phthalate (MEHP)** is the primary, active metabolite of DEHP. Phthalates are lipophilic and may accumulate in adipose tissue. MEHP accumulation, in particular has been found to impact lipolysis and glucose uptake/glycolysis in fat cells (73).
Polycyclic Aromatic Hydrocarbons	PAHs/Benzo(a)pyrene	Air, Water, Food	Industrial chemicals; By-products of erupting volcanoes and forest fires	**Polycyclic aromatic hydrocarbons (PAHs)** do not refer to a single compound, but instead cover a wide range of complex mixtures, which are often produced during incomplete combustion of organic matter. **Benzo[a]pyrene** belongs to this group of PAHs and is regarded by the EPA as a priority pollutant (16). Long-term exposure to PAHs, particularly benzo[a]pyrene can result in a number of adverse health effects in humans. PAHs have been detected in adipose samples, and benzo[a]pyrene is regarded as a probable carcinogen (16).
Polychlorinated naphthalenes	PCNs	Soil, Air, Water, and Food	Industrial chemicals; By-products during production of PCBs	**Polychlorinated naphthalenes (PCNs)** are industrial chemicals that until the 1970s were in high production and most commonly used as wood preservatives and insulating coatings for electrical wires and plastic additives (87). In addition, PCNs can be released as by-products of waste incineration or PCB production, and many PCNs still persist, unchanged, in the environment. The family of PCNs consists of approximately 75 chlorinated naphthalenes that are polychlorinated and structurally similar to PCBs. As a result of this structural similarity, PCNs share many physical and chemical properties with PCBs, including high lipophilicity, great stability, and high resistance to biodegradation. As a result, the toxicity profiles of PCNs also resemble those of most coplanar PCB congeners.
Pentachlorophenol	PCP	Soil, Air, Water, and Food	Insecticide; By- products of chemical metabolism	**Pentachlorophenol (PCP)** exists in two forms, one as pure PCP, and the other as its sodium salt. PCP was initially introduced in the 1930s and has been used as an insecticide, herbicide, fungicide, and disinfectant. However, as a consequence of its toxicity profile, PCP use has significantly decreased. Although data is limited on the distribution of PCP in humans, there are a few reports that indicate that PCP can be absorbed by the liver, adipose, and other tissues (133) (259). The binding of PCP to plasma proteins also plays a vital role in PCP distribution (55) (130). Hexachlorobenzene and hexachlorocyclohexane are metabolized to pentachlorophenol.
Perfluorinated compounds	PFCs/PFAS	Food	Industrial chemicals	**Perfluorinated compounds (PFCs)** are a diverse family of compounds containing fluorine atoms. They have a number of applications, including use in textiles, kitchen ware, and food packaging materials. They are highly persistent in the environment and bioaccumulate in people and wildlife (295) (60) (125) (188).

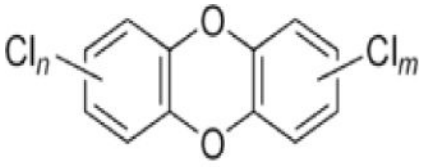
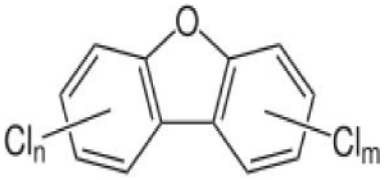
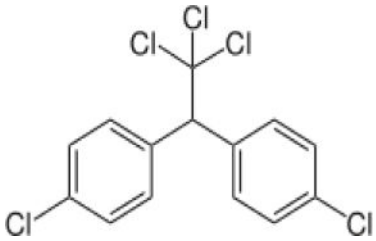
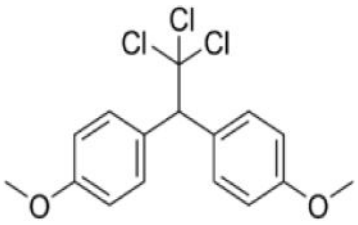
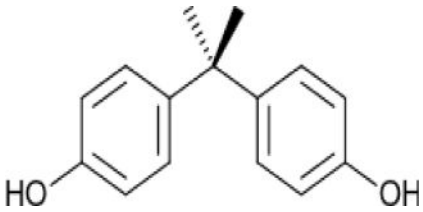
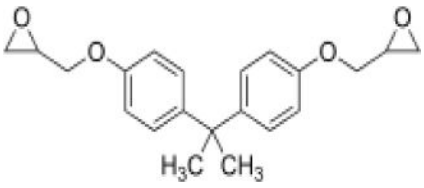
Table 3

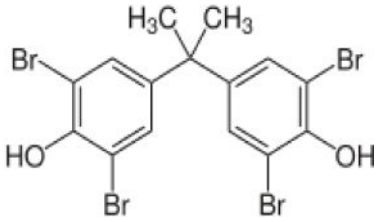
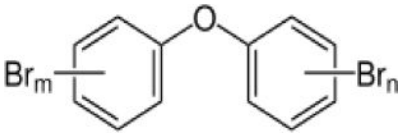
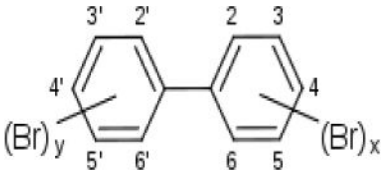
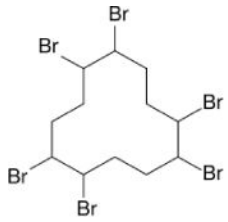
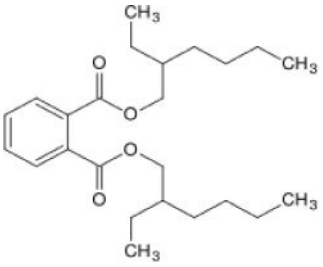
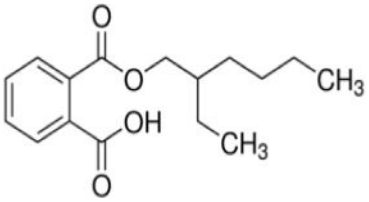
Summary of Toxicant Structures and Partition Coefficients

Compound	General Structure	Partition Coefficient (Log K_{ow} or Log P)	References
Hexachlorobutadiene (HCBD)		4.78	(141)
Aldrin		5.17–7.40	(327)
Dieldrin		3.69–6.20	(327)
Endrin		3.21–5.34	(327)
Chlordane	 *cis*-chlordane	6	(327)
Endosulfan		3.83 (α isomer); 3.62 (β isomer)	(141)

Compound	General Structure	Partition Coefficient (Log K_{ow} or Log P)	References
Toxaphene		3.23–5.50	(327)
Heptachlor		4.40–5.50	(327)
Mirex		6.89	(412)
Chlordecone		5.41	(141)
α-/β-Hexachlorocyclohexane (HCH)	 *alpha-* *beta-*	3.78	(141)
Lindane (γ-HCH)		3.8	(141)

Compound	General Structure	Partition Coefficient (Log K_{ow} or Log P)	References
Pentachlorobenzene (PeCB)		5.18	(141)
Hexachlorobenzene(HCB)		3.03–6.42	(327)
Pentachlorophenol (PCP)		5.12; PCP sodium salt: 1.3 at pH 10	(66) (141)
Polycyclic aromatic hydrocarbons (PAHs)		3.30–6.84	(141) (253)
Polychlorinated naphthalenes (PCNs)	 m and n can range from 0 - 4	3.90–8.3	(87)
Polychlorinated biphenyls (PCBs)		4.30–8.26	(327)

Compound	General Structure	Partition Coefficient (Log K_{ow} or Log P)	References
Polychlorinated dibenzo-p-dioxins (PCDDs)	 *n* and *m* can range from 0 - 4	4.75–8.20	(327)
Polychlorinated dibenzofurans (PCDFs)	 *n* + *m* can range between 2 - 8	4.9–6.92	(356)
Dichlorodiphenyl-trichloroethane (DDT)		4.89–6.91; 3.88–8.18	(158) (327)
Methoxychlor		4.68–5.08	(159)
Bisphenol A		3.32	(141)
Bisphenol A diglycidyl ether (BADGE)		3.84	(268)

Compound	General Structure	Partition Coefficient (Log K_{ow} or Log P)	References
Tetrabromobisphenol A (TBBPA)			
Polybrominated diphenyl ethers (PBDEs)			
Polybrominated		6.39 (Hexabromo–	
biphenyls (PBBs)		biphenyl)	
Hexabromo-cyclododecane (HBCD)		5.6	
Di-(2-ethylhexyl) phthalate (DEHP)		7.6	
Mono-(2-ethylhexyl) phthalate (MEHP)		4	(170)

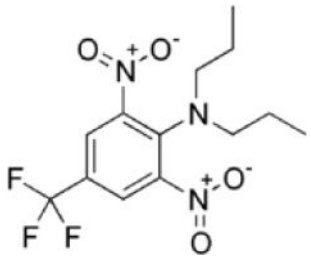
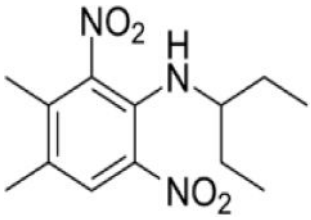
Compound	General Structure	Partition Coefficient (Log K_{ow} or Log P)	References
Trifluralin		5.34	(141)
Pendimethalin		5.2	(392)

Table 4

Toxicant Levels in Human and Aquatic Samples

Compound	Toxicant Concentrations				Study Population	References
	Adipose	Breast Milk	Blood Serum	BCF		
Aldrin	0.048 ppb	0.003 ppb	0.004 ppb	—	Women in Delhi	(286)
	Mean: 7.2 ng/g fat vAT; Mean: 22.7 ng/g fat scAT	—	—	—	Obese men and women in Portugal undergoing bariatric surgery	(389)
	—	—	—	350 44,600	Freshwater Fish	(184)
	0.0014 mg/g	—	—	—	Men and women in Korea	(307)
	0.042–0.173 ppm	—	—	—	Men and women in Jordan (ages	(25)
					0–60yrs old)	
	Mean: 25.56 ng/g lipid Max.: 137. 2 ng/g lipid	—	Mean: 2.17 ng/mL Max.: 14.16 ng/mL	—	Post-menopausal women in Spain	(52)
Dieldrin	—	—	—	2,385–68,286	Freshwater Fish	(17)
	0.099 ppb	0.060 ppb	0.002 ppb	—	Women in Delhi	(286)
	Mean: 65.2 ng/g fat vAT; Mean: 45.1 ng/g fat scAT	—	—	—	Obese men and women in Portugal undergoing bariatric surgery	(317)
	—	0.54 mg/kg	—	—	Women in Canada (1975)	(119)
	Mean: 0.029 mg/kg scAT; Max.: 145 ng/g scAT	—	—	—	Men and women in Canada (1983–1984)	(119)
	0.0001 mg/g	—	—	—	Men and women in Korea	(307)
	0.04–0.27 ppm	—	—	—	Men and women in Jordan (ages 0–60yrs old)	(25)
	Mean: 17.01 ng/g lipid Max.: 84.05 ng/g lipid	—	Mean: 1.21 ng/mL Max.: 6.35 ng/mL	—	Post–menopausal women in Spain	(52)
	0.24 ppm	—	—	—	US individuals with non-Hodgkin’s Lymphoma	(323)
	0–15 ng/g fat	—	—	—	Women in Hong Kong	(322)
Chlordane	—	—	—	3,000–12.000	Marine Fish	(435)
	—	—	—	18,500	Freshwater	(301)
					Fish	
	Chlordane: 4.5–49 ng/g fat; Oxy-chlordane: 11–75 ng/g fat; Nonachlor: 29–230 ng/g fat	—	—	—	Men and women in Japan	(153)
	Mean: 0.012 mg/kg scAT; Max.: 91 ng/g scAT	—	—	—	Men and women in Canada	(119)
	Oxy-chlordane: Mean: 200 ng/g fat; Trans-nonachlor: Mean: 140 ng/g fat	—	—	—	Men and women in Ontario, Canada	(97)
	Oxy-chlordane: 40.9 ng/g fat; Trans-nonachlor: 45.9 ng/g fat	—	—	—	Women in Long Island, New York without breast cancer	(372)
	Oxy-chlordane: 12 ng/g lipid; Trans-nonachlor: 32 ng/g lipid	—	—	—	Men and women in Finland	(24)
	Oxy-chlordane: 0.20 ppm	—	—	—	US individuals with non-Hodgkin’s Lymphoma	(323)

Compound	Toxicant Concentrations				Study Population	References
	Adipose	Breast Milk	Blood Serum	BCF		
Endrin	—	—	—	2,000–10,000	Freshwater Fish	(9)
	—	—	—	4,800–6,000	Saltwater Fish	(9)
	Mean: 284.8 ng/g fat vAT; Mean: 146.4ng/g fat scAT	—	—	—	Obese individuals in Portugal	(317)
	0.003 μg/g fat	—	—	—	Men and women in Korea	(307)
	0.061–0.358 ppm	—	—	—	Men and women in Jordan (ages 0–60yrs old)	(25)
	Mean: 47.43 ng/g lipid, Max.: 148.13 ng/g lipid	—	Mean: 2.25 ng/mL; Max.: 6.24 ng/mL	—	Post-menopausal women in Spain	(52)
Heptachlor	—	—	—	10,630	Clam Fat	(10)
	—	—	—	2,570	Soft Clams	(10)
	—	—	—	8,511	Oysters	(10)
	—	Heptachlor epoxide: 0.60 mg/kg	—	—	Women in Canada (1975)	(119)
	Mean: 0.083 mg/kg fat Max.:116 ng/g fat	—	—	—	Men and women in Canada (1983–1984)	(119)
	Heptachlor epoxide: 41 ng/g fat	—	—	—	Men and women in Ontario, Canada	(97)
	0.086–0.173 ppm	—	—	—	Men and women in Jordan (ages 0–60yrs old)	(25)
	Heptachlor epoxide 0.14 ppm	—	—	—	US individuals with non-Hodgkin's Lymphoma	(323)
	Heptachlor epoxide: 0–11 ng/g fat	—	—	—	Women in Hong Kong	(322)
Mirex	—	—	—	15,000	Rainbow trout	(13)
	0.04 mg/kg fat scAT	—	—	—	Men and women in Canada (1980–1981) (ages 0–102yrs old)	(119)
	Mean: 116 mg/kg lipid scAT Mean: 126 mg/kg lipid omental fat	—	—	—	Men and women in Greenland	(103)
Toxaphene	—	—	—	4,247–76,000	Fish	(15)
Compounds detected include toxaphene congeners 2, 26, 38, 40/41, 44, 50, and 62	Sum of toxaphenes: 0.82–17 ng/g lipid	—	—	—	Swedish population (n=8)	(112)
Methoxychlor	—	—	—	195–1500	Fish	(12)
	0.68 μg/kg	—	—	—	Harp Seals (blubber)	(12)
	Mean: 21.3 ng/g fat vAT; Mean: 40.6 ng/g fat scAT	—	—	—	Obese men and women in Portugal undergoing bariatric surgery	(317)
	Mean: 39.86 ng/g lipid; Max.: 155.58 ng/g lipid	—	Mean: 0.38 ng/mL; Max.: 0.39 ng/mL	—	Post-menopausal women in Spain	(52)
	347.73 ng/g fat	—	—	—	Women undergoing C-section in southern Spain	(181)
Endosulfans (alpha/beta isomers)	—	—	—	17.1–11,583	Fish	(8)
	Endosulfan I: 2.8 ng/g fat vAT; 47 ng/g fat in scAT Endosulfan II: 1.8 ng/g fat vAT 2.2ng/g fat scAT	—	—	—	Obese men and women in Portugal	(317)

Compound	Toxicant Concentrations				Study Population	References
	Adipose	Breast Milk	Blood Serum	BCF		
	Endosulfans I/II: Mean: 21.37 ng/g lipid; Max.: 417.5 9 ng/g lipid	—	Endo-sulfans I/II: Mean: 8.85 ng/mL; Max.: 210.99 ng/mL	—	Post-menopausal women in Spain	(52)
	Endosulfan I: Mean 75.46 ng/g fat Endosulfan II: Mean: 51.68 ng/g fat	—	Endo-sulfan I: Mean: 1.27 ng/mL Endo-sulfan II: Mean: 76.38 ng/mL	—	Women undergoing C-section in southern Spain	(181)
Chlordecone	—	—	—	>60,000	Fish	(13)
α-Hexachlorocyclohexane (α-HCH)	Mean: 0.016 mg/kg fat	—	—	—	Men and women in Poland	(251)
β-Hexachlorocyclohexane (β-HCH)	34.25 + 43.2 mg/kg fat	—	—	—	Obese population	(72)
	Median: 64.7 ng/g vAT Median: 72.2 ng/g scAT	—	—	—	Obese men and women in Portugal	(317)
	Mean: 0.228 mg/kg fat Median: 0.120 mg/kg fat	—	—	—	Men and women in Poland	(251)
	189, 424, 253 ng/g fat	—	—	—	Men and women from Southeast China	(419)
Hexachlorobenzene (HCB)	0.553 ppb	—	—	—	USA Population	(330)
	23.4 + 3.17 mg/kg	—	—	—	Obese population	(72)
	—	—	—	17,000,0 00; 21, 900	Lichens; Fish	(282) (412)
	Mean: 0.310	—	—	—	Men and	(251)
	mg/kg fat Median: 0.120 mg/kg fat				women in Poland	
	16.3, 39.4, 23.9 ng/g fat	—	—	—	Men and women from Southeast China	(419)
Dichlorodiphenyl-trichloroethane (P,P′-DDT)/Dichlorodiphenyl-dichloroethylene (p,p′-DDE)	p,p′-DDE: 512.2 + 284 mg/kg	—	—	—	Obese population	(72)
	p,p′-DDE: 610 ng/g lipid	—	—	—	Men and women in Finland	(24)
	p,p′-DDE: Mean: 5.745 mg/kg fat Median: 4.382 mg/kg fat Max.: 35.850 mg/kg fat	—	—	—	Men and women in Poland	(251)
	p,p′-DDT : Mean: 0.537 mg/kg fat Median: 0.478 mg/kg fat	—	—	—	Men and women in Poland	(251)
	p,p′-DDE: 18.3, 11.5, 9.86 ng/g fat	—	—	—	Men and women from Southeast China	(419)
	p. p′-DDE: Median: 93.0 ng/g lipid	—	175.7 ng/g lipid	—	Men and women in southern Spain	(33)
	p,p′-DDE: Median: 22.6 ng/g vAT Median: 2.8 ng/g scAT	—	—	—	Obese men and women in Portugal	(317)
Pentachlorobenzene (PeCB)	0–70 ng/kg	—	—	—	Canadian Men and Women	(261)
	0–146 mg/kg	0–25 mg/kg	—	—	Men and Women in the Republic of Slovenia (between ages 20–60)	(178)
Lindane (γ-HCH)	Median: 19.0 ng/g vAT Median: 31.0 ng/g scAT	—	—	—	Obese men and women in Portugal	(317)
	Mean: 0.074 mg/kg fat	—	—	—	Men and women in Poland	(251)
	0.210, 0.130, 0.620 ng/g fat	—	—	—	Men and women from Southeast China	(419)
Hexachlorobutadiene (HCBD)	0.004 mg/g	—	—	—	Canada	(267)
Trifluralin	0.170, 0.620, 7.17 ng/g fat	—	—	—	Men and women from Southeast China	(419)

Compound	Toxicant Concentrations				Study Population	References
	Adipose	Breast Milk	Blood Serum	BCF		
Pendimethalin	0.9 ppm	—	—	—	Royal Hart Wistar Rats	(438)
Polycyclic Aromatic Hydrocarbons (PAHs)	11–2,700 ng/g	—	—	—	General population (n=4)	(293)
Compounds detected: anthracene, pyrene, benzo[e]pyrene, benzo[k] fluoranthene, benzo[a]pyrene, and benzo[g,h,i]perylene	15–361 ng/g lipid	—	—	—	Women in Korea	(277)
Tetrabromobisphenol A (TBBPA)	not detected	0.06–37.34 ng/g lipid	154 pg/g fresh weight (maternal serum) 199 pg/g fresh weight (cord serum)	—	French women and their newborns	(64)
Polychlorinated dibenzo-p-dioxins (PCDD)/Polychlorinated dibenzofurans (PCDF)	33.9–504 pg/g lipid Mean: 108 pg/g lipid	—	—	—	General Population in China	(353)
	Fertile men: 3.0–15.8 pg/g fat Infertile men: 2.8–17.2 pg/g	—	—	—	Men in Ankara, Turkey	(81)
	16–56 pg/g, fat weight	—	—	—	Women in India	(210)
	14–46 pg/g, fat weight	—	—	—	Men in India	(210)
	—	—	0.1–3,270 ppt	—	Adult men and women in the US	(147)
Bisphenol F diglycidyl ether (BFDGE)	19.1–4,500 ng/g wet weight	—	—	—	Men and women in the US	(418)
Polybrominated diphenyl ethers (Compounds detected included hexa-, hepta-, tetra-, and penta-BDEs)	17–9,630 ng/g lipid weight Mean: 399 ng/g lipid weight	—	—	—	New York, NY population	
	—	6.2–419 ng/g (or ppb) lipid Mean: 73.9 ng/g lipid	—	—	U.S. Mothers	(342)
	—	—	—	115,000–1,440.00 0 (based on lipid weights)	Guppies	(129)
Mono-(2-ethylhexyl)phthalate (MEHP)–(metabolite of DEHP)	—	—	Max.: 19,740 ±1,670 (one sample)	—	Rats	(78)
Polychlorinated naphthalenes (PCN) (Compounds detected included tetra-, penta-, and hexa-, congeners)	0.9–34.6 ng/g fat	—	—	—	Children in Germany, Russia, and Kazakhstan	(427)
	0.04–1.09 ng/g lipid	—	—	—	Men and women in Sweden	(425)
	—	483–3081	—	—	Women in Sweden	(252)
		ng/kg				
	—	—	1,150–30,400 ng/kg	—	Individuals in Taiwan after exposure incident	Values reported by (87)
(Compounds detected included mono- to tetra-, congeners)	—	—	—	0–33,884	Fish	Values reported by (87)
Hexabromobiphenyl	1–2 ppb	—	—	—	General Population in US	(233)
	Perirenal fat: 475 ng/g	—	—	—	Individuals in US after exposure incident	(270)
		—	—	18,100	Fathead Minnows	(412)
Hexabromo-cyclododecane (HBCD)	—	—	—	708,000 (lipid weight-based)	Guppies	(129)
	2.4–38.1 ng/g, lipid weight	—	—	—	Fish	(352)
	Blubber: 7.38 ng/g, lipid weight	—	—	—	Dolphin	(182)
	0.333 ± 0.571 ng/g, lipid weight	—	—	—	Men and women in the US	(182)

Compound	Toxicant Concentrations				Study Population	References
	Adipose	Breast Milk	Blood Serum	BCF		
Pentachlorophenol (PCP)	Median: 0.013 mg/g	—	0.005–0.069 mg/mL	—	Men and Women in Northern Bavaria	(133)
		—	884 mg/L	—	Men, women, and children (ages 8–60)	(259)
Polychlorinated biphenyls (PCBs) (Compounds detected include bi- to deca-chlorobiphenyls)	—	—	—	2.64–5.97 (log BCF)	Fish	Reported by (162) as published by (118) (129) (375) (338) (287)
	Range: 97–768 ng/g fat Median: 235	—	—	—	Stillbirths in the US	(219)
	ng/g fat					
	Mean: 0.856 mg/kg fat Max.: 36 mg/kg fat	—	—	—	Men and women in Poland	(251)
	PCB-153: 310 ng/g lipid	—	—	—	Men and women in Finland	(24)
	Dioxin-like PCBs: 4.1–125 ng/g lipid Mean 32.8 ng/g lipid	—	—	—	General population in China	(353)
Bisphenol A (BPA) Chlorinated derivatives detected: monochloro-BPA (ClBPA), dichloro-BPA (Cl_2BPA), and trichloro-BPA (Cl_3BPA)	BPA: 5.83 ± 3.48 ng/g; ClBPA: 3.05 ± 0.28 ng/g; Cl_2BPA: 9.21 ± 9.26 ng/g; Cl_3BPA: 0.74 ± 0.15 ng/g	—	—	—	Women in Spain	(116)
Di-(2-ethylhexyl) phthalate (DEHP)	—	—	—	3, 173 ± 3,149	Algae	(288)
	—	—	—	1,4693 ± 949	Mollusks	(288)
	—	—	—	1,164 ± 1,182	Crustaceans	(288)
	—	—	—	1,058 ± 772	Insects	(288)
	—	—	—	422	Polychaetes	(288)
	—	—	—	280 ± 230	Fish	(288)
	—	—	—	605	Amphibians	(288)
	0.25 to 9.85 mg/kg	—	—	—	Chicks	(179)

Table 5

Summary of the Effects of POPs on AT Function

Class	Compound	Effect on Adipocyte Differentiati on	Effect on Lipogenesis	Effect on Adipokine Release	Effect on Glucose Uptake	Effect on Lipolysis
Organochlori nes	TCDD	Low dose increase, high dose decrease (34) Decrease (56) (71) (354) (161)	Decrease (56) (302) Decrease (195)	Increase inflammatory (195) (235) (292) (204) Increase leptin, adiponectin (385)	Decrease (195) (292)	Increase (235) (157)
	PCBs	Low dose increase, high dose decrease (PCB-77) (34) Decrease (PCB-126) (121) Increase (PCB-153) (69) (385)		Increase inflammation (PCB-77) (34) (204) Increase leptin, adiponectin (PCB-153) (385)	Decrease (336) Decrease (37)	
	PCDDs PCDFs				No effect (336)	
	DDT/DDE	Increase (DDT) (278) Increase (DDE) (69)	Increase (160)	Increase leptin, adiponectin, resistin (DDE) (160) Increase leptin, adiponectin (385)	Decrease (336)	
	HCB		Decrease in BAT (29)			
	Oxy- chlordane, dieldrin		Increase (160)			
BFRs	HBCD				Decrease (431)	
	PDBE	Increase (397)			Decrease (155)	Increase (155)
	BDE-47	Increase (185)				
Phthalates	DEHP	Increase (62)	Increase (373)	Increase inflammatory (62)		
	MEHP	Increase (142) (115) (385)	Increase (142)	Increase leptin, adiponectin (385)	Increase (73)	Increase (73)
BPA/BADGE	BADGE	Increase (67)				
	BPA	Increase (67) (433) (297) (385)	Increase (258) (433) (32)	Increase inflammatory (433) (32) (404) Decrease adiponectin (264) (166)	Decrease (404) (32)	
PAH	Benzo[a]pyrene					Decrease (173) (172)
	Air pollution		Increase (377)			
	PAH				Decrease (198)	

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Table 6

POP Mechanisms of Action in AT

Pathway	Normal function in adipose tissue	Purported disruptors	Impacts of disruption
PPARγ	Increase adipogenesis, increase lipogenesis, increase glucose uptake	Phthalates Organotins BFRs?	Promote adipogenesis
AhR	Xenosensor, regulation of lipogenesis	Dioxins PCBs PAHs BFRs?	Wasting syndrome Increased body weight, increased fat mass, increased inflammatory response, impaired glucose tolerance
ER	Inhibit lipogenesis, reduce body weight/fat mass, maintain glucose homeostasis	BPA	Prenatal exposure linked to increased body weight and adiposity in adults
		AhR interaction	Inhibition of normal estrogen function to reduce body weight and adiposity
AR	Promote glucose uptake	DDE, PCBs	Insulin resistance
TR	Regulation of lipid mobilization and storage	BFRs AhR interaction	Unknown

Table 7

Prenatal POP Exposure and Associations with Obesity

Class	Compound(s) Studied	Population	Finding	Reference
Organochlorines	PCBs, DDE	Mothers of Michigan fisheaters cohort and their daughters	Prenatal exposure to DDE associated with increased offspring BMI. Prenatal PCB had no effect.	(189)
	PCBs, DDE, HCB	Rhea study of pregnant women and their children in Greece.	Prenatal exposure to HCB associated with BMI, obesity, abdominal obesity, greater skinfold thickness, and systolic BP. Prenatal DDE associated with BMI, abdominal obesity, and diastolic BP. PCBs not associated with offspring obesity.	(402)
	PCB, DDE	Mother-child pairs from ENRIECO cohort	Postnatal NDL PCB-153 associated with a decrease in weight-for-age z-score. Prenatal DDE associated with increased weight-for- age z-score.	(174)
	Dioxins, PCBs, lead, HCB, DDE, HCH	Russian Children's Study: young boys. Background exposure.	Early exposure. Serum HCB, β-HCH, DDE negatively associated with 4 year follow-up BMI in boys.	(58)
	PBB and PCB	Daughters of women in the Michigan PBB cohort.	Prenatal PCB exposure negatively associated with weight for height females.	(47)
	PCBs, PBB, DDT	Women and children in Michigan at risk for PCB exposure	Prenatal PCB associated with lower weight at 4 years.	(176)
	PCB, DDE, DDT	Mothers and African American children of National Collaborative Perinatal Project (NCPP). Background exposure.	Maternal levels of dioxin-like PCBs negatively associated with girl's weight. Non-dioxin-like PCBs (PCB 15) not associated with girl's weight. Maternal levels of dioxin-like PCBs marginally associated with boy's weight.	(214)
	PCBs	Pregnant women of CHDS prospective cohort study. Background exposure.	Maternal PCBs associated with lower birth weight in males.	(151)
	PCBs, DDE, DDT, HCB	AMICS-INMA Spanish cohort of pregnant women and children. Background exposure.	Maternal PCB and DDE associated with overweight in females but not in males. DDT associated with overweight in males but not associated in females.	(408)
	PCBs, DDE	Mothers and newborns in Belgium. Background exposure.	Maternal DDE and PCBs associated with BMI 1-3 years.	(414)
	DDE, DDT	Mothers and male children with normal birth weights in Mexico. Background exposure.	Prenatal DDE exposure no association with BMI in males.	(89)
	PCBs and DDE	North Carolina Infant Feeding Study children. Background exposure.	Maternal transplacental DDE positively associated with weight in boys but not girls at 14yrs old. Lactational and trasnsplacental PCBs and lactational DDE not associated with weight.	(127)
	DDE, HCB, β- HCH, NDL PCB	INMA cohort in Spain. Background exposure.	Maternal serum: Prenatal DDE associated with BMI z-scores at 14 months and rapid growth (stronger association in boys). Other OCs (HCB, β-HCH, and NDL PCB) not associated with BMI.	(265)
	PCBs, DDE	Mothers of Michigan fisheaters cohort and their daughters.	Prenatal DDE associated with BMI and BW in adult female offspring.	(189)

Class	Compound(s) Studied	Population	Finding	Reference
			Prenatal PCBs not associated with BMI in adult female offspring.	
	DDE, DDT	CPP study mothers and male offspring. Background exposure.	Prenatal DDE and DDT from breastmilk not associated with BMI in boys.	(126)
	DDT, DDE	CHAMACOS cohort of pregnant women and children in California. Background exposure.	Maternal DDE and DDT not significantly associated with BMI and did not significantly increase odds of overweight and obesity.	(422)
	HCB, PCBs, DDE, DDT	Mothers and children in Asthma Multicenter Infants Cohort in Spain. Background exposure.	Maternal HCB associated with higher BMI and increased risk of being overweight and obese at age 6.5yrs old.	(362)
	PCB, DDE	Mother-child pairs fromFaroe Islands. Background exposure.	Prenatal PCB associated with BMI and waist circumference in 7yr old girls with overweight mothers. In girls with normal weight mothers, PCBs were associated with increased WC but not associated with BMI. In girls with overweight mothers, DDE was associated with WC at 7yrs old. No associations between PCB or DDE and BMI in 5yr old girls. No associations in boys.	(383)
	PCB 153, DDE	European birth cohorts. Background exposure.	PCB-153 cord serum inversely associated with birth weight. DDE not associated with birth weight.	(131)
	Phthalates, BPA, PCBs, HCH, HCB, PBDE	Pregnant Spanish birth cohort study of Environment and Childhood project. Background exposure.	Exposure to HCB, β-HCH, PCB 138 (NDL), PCB 180 (NDL) associated with increased BMI at age 7. DDE not significantly associated with increased BMI. HCB, β-HCH, NDL PCBs, and DDE associated with increase in overweight at age 7.	(21)
	PCBs, PCDD, PCDF,	Caucasian mother- infant pairs in Netherlands. Background exposure.	NDL PCBs in cord plasma and maternal plasma negatively associated with birth weight and growth rate 0-3 months in formula fed babies but not body fat.	(308)
	NDL PCBs, DL PCBs, DDE, HCB	14-15yr old Flemish adolescents. Background exposure.	Serum DL PCBs associated with increased BMI and NDL PCBs and HCB associated with decreased BMI at puberty in males and females. DDE not associated with BMI.	(104)
	DDE, HCB, NDL PCBs	INMA birth cohort in Spain. Background exposure.	Prenatal DDE and HCB associated with rapid growth 0-6 months and overweight at 14 months. PCBs not associated with rapid growth or overweight.	(405)
	DDE, phthalates, NDL PCB	Dutch mother- daughter pairs. Background exposure.	Maternal DDE associated with increased BMI 6-11 months. NDL PCB not associated with BMI.	(95)
	DDE, HCB, NDL PCBs	Spanish mother-child pairs	Maternal HCB and DDE associated with rapid growth and overweight. PCBs not associated with postnatal growth.	(407)
	DDE, DDT, PCBs, HCH	CPP mother-child pairs in US. Background exposure.	Prenatal HCB, heptachlor, β-HCH, DDE, total PCBs, trans-nonachlor, and oxychlordane not associated with obesity or BMI at age 7. Dieldrin associated with obesity but not BMI.	(90)
	NDL PCBs, DDE, HCB	Flemish mother-child pairs from FLEHS I	Prenatal DDE associated with WC and waist/height ratio in girls. PCBs,	(101)

Class	Compound(s) Studied	Population	Finding	Reference
			dioxins, HCB not associated with WC.	
	DDE, DDT	American mother- child pairs in CHAMACOS study	In boys, prenatal DDT associated with BMI, WCz-scores, and overweight/obesity at 9yrs old. DDE not associated. Girls not associated.	(423)
	PCB, DDE, HCB	Danish children in EYHS study	PCBs, DDE, HCB in 8-22yr olds not associated with obesity.	(384)
	DDT, DDE, HCB, β-HCH, total PCBs	Mother-child pairs in Spain. Background exposure.	Prenatal DDT and DDE associated with decreased birth weight. HCB, β-HCH, PCB not associated.	(248)
	PCBs	Mother-child pairs in NY. Background exposure.	Preconception PCBs associated with reduced birth weight.	(284)
Poly-brominated flame retardants (BFRs)	PBDE	Pregnant Long-Evans hooded rats dosed with 1 or 10mg/kg bodyweight PBDE- 99	Prenatal exposure to PBDE-99 increased rat offspring birth weight.	(238)
	PBB and PCB	Daughters of women in the Michigan PBB cohort.	Moderate (but not high) prenatal PBB exposure associated with increased weight for height in females.	(47)
	Phthalates, BPA, PCBs, HCH, HCB, PBDE	Pregnant Spanish birth cohort study of Environment and Childhood project. Background exposure.	PBDE not associated with child weight status.	(21)
	PBDE	Mexican-American mother-child pair of CHAMACOS study	Maternal PBDE associated with decreased BMI z-scores in girls but NS in boys. Child's serum BDE-153 negatively associated with BMI and WC at 7yrs old in both sexes.	(113)
	PBDE	Mexican-American mother-child pairs of CHAMACOS	Maternal PBDEs associated with lower birth weight, but effect is nonsignificant when maternal weight gain is included.	(144)
Polycyclic Aromatic Hydrocarbons (PAHs)	PAH	MOCEH study in Korea without diabetes	Consumption of foods high in PAH (i.e. grilled or roasted meat) associated with reduced birth weight.	(215)
	PAH	Birth cohort in Poland, nonsmoking mothers.	Maternal dietary and airborne PAH exposure associated with reduced birth weight.	(180)
	PAH	Birth cohort in Poland. Background exposure.	Newborn PAH-DNA adduct levels associated with reduced birth weight.	(315)
	PAH	Birth cohort in Poland. Background exposure.	Newborn PAH-DNA adduct levels associated with reduced birth weight.	(314)
	PAH	Krakow Caucasians, NYC African Americans, NYC Dominicans	Relatively low levels of prenatal PAH exposure associated with reduced birth weight.	(76)
	PAH	NHANES 2003-2008 16-18yr olds	PAH metabolites associated with BMI and WC in 6-18yr olds. High exposure to both PAH and environmental tobacco smoke associated with increased obesity as compared to low-PAH, low-ETS.	(197)
	PAH	African-Americans and Hispanic children and mothers in NY	Prenatal PAH exposure associated with higher childhood BMI and risk for obesity at 5-7yrs old.	(335)
	PAH	NHANES 2001-2006 6-19yr olds	Early exposure: mass sum of PAH associated with BMI z-score, WC, and obesity.	(346)

Class	Compound(s) Studied	Population	Finding	Reference
Phthalate Esters	Phthalates, BPA	Korean girls 6-14yrs old	Early exposure 6-14yr old female: urine MEP not associated with childhood obesity. Urine PA associated with obesity. Serum MEP, PA, and DBP associated with childhood obesity.	(77)
	Phthalates	NHANES 1999-2002. Background exposure.	Early exposure: serum MEP associated with BMI and WC in 12-19yr old females, but not associated in 6-11yr old males or females, or in 12-19yr old males. MEHP associated with decreased BMI in 12-19yr old females, not associated in 6-11 males and females, or in 12-19yr old males. MBP and MEOHP were not associated with BMI.	(145)
	Phthalates, BPA	Girls in US	MEP, MEHHP, MEHP, MECPP, MBzP, MiBP, MCPP, MBP, and MEOHP not associated with BMI in 6-9yr old girls.	(428)
	Phthalates, BPA, PCBs, HCH, HCB, PBDE	Pregnant Spanish birth cohort study of Environment and Childhood project. Background exposure.	Phthalates inversely associated with overweight.	(21)
	Phthalates	INMA Spanish birth cohort. Background exposure.	High MW phthalate metabolites associated with lower weight gain and BMI z-score in boys and higher BMI in girls. Low MW metabolites not associated with BMI or weight gain.	(406)
	Phthalates	Hispanic and Black NY children 6-8yrs old	Early exposure: MEP and low MWP associated with BMI and WC in overweight children but not normal weight children.	(388)
	Phthalates	NHANES 2003-2008	Early exposure: Low MW metabolites (Mn BP, MEP, and MiBP) associated with obesity in male children and adolescents. Not associated for high MW and obesity	(59)
	DDE, phthalates, NDL PCB	Dutch mother-daughter pairs. Background exposure.	Maternal exposure to low exposure of MEOHP (DEHP metabolite) associated with higher BMI.	(95)
	Phthalates	Mother-child pairs in China	Prenatal DBP associated with low birth weight.	(436)
	Phthalates	Children 4-9yrs old in Denmark without diabetes	Urinary MEHP (percent of DEHP metabolites excreted as MEHP) associated with wetght.	(48)
Bisphenol A and Bisphenol A diglycidyl ether (BADGE)	BPA	RHEApregnancy cohort in Greece	BPA levels at 4 years associated with BMI and WC. Prenatal BPA negatively associated with BMI and adiposity in girls and positively in boys.	(403)
	Phthalates, BPA	Girls in US	BPA associated with decreased BMI in 6- 9yr old girls.	(428).
	Phthalates, BPA, PCBs, HCH, HCB, PBDE	Pregnant Spanish birth cohort study of Environment and Childhood project. Background exposure.	BPA not associated with child weight status.	(21)
	BPA	CHAMACOS study in California birth cohort. Background exposure.	Prenatal urinary BPA inversely associated with BMI and %body fat at 9 years in girls but not boys.	(143)

Class	Compound(s) Studied	Population	Finding	Reference
			Urinary BPA at 5 years not associated with BMI. Urinary BPA at 9 years positively associated with BMI, body fat, and overweight/ obesity.	
	BPA	INMA birth cohort in Spain. Background exposure.	BPA weakly associated with increased WC at 4 years but not associated with BMI or WC at earlier ages.	(405)
	Phthalates, BPA	Korean girls 6-14yrs old	Early exposure 6-14yr old females: urine BPA not associated with childhood obesity.	(77)
	BPA	Chinese school children 8-15yrs old. Background exposure.	Early exposure: BPA associated with BMI in males and females.	(417)
	BPA	2003-2008 NHANES children 6-9yrs old	Early Exposure: BPA associated with obesity and BMI z-score.	(394)
	BPA	Mother-child pairs with or without occupational BPA exposure	Maternal exposure to BPA in workplace associated with decreased birth weight.	(269)

Table 8

Adult POP Exposure and Associations with Obesity

Class	Compound(s) Studied	Population	Finding	Reference
Organochlorines	OC pesticides, PCBS, PBB, DDE, DDT	CARDIA prospective study in young adults without diabetes. Background exposure.	Serum p, p'-DDE, p, p'- DDT, and some PCB congeners predicted BMI. Several PCB congeners nonlinearly associated with increased BMI. Oxychlordane, trans-nonachlor, HCB, β- HCH, Mirex not associated with BMI.	(230)
	Dioxins, dioxin-like PCBs, non-dioxin-like PCBs, DDE, β-HCH, OC pesticides	NHANES 1999- 2002. Adults without diabetes. Background exposure.	PCDD, DDE, β-HCH and PCBs associated with waist circumferences. NDL PCB inverted U-shaped association with WC.	(223)
	Dioxin, PCBs	Cross-sectional study of general population in Japan with and without diabetes	Dioxins and PCBs associated with MS.	(399)
	PCDDs, PCDFs, PCBs, OC pesticides	NHANES 1999- 2002 adults with background exposure.	HpCDD, OCDD, and DDE positively associated with BMI. PCB 153 negatively associated with BMI. Oxychlordane, trans- nonachlor not associated with BMI.	(224)
	HCH, HCB, OC pesticides, TCDD, DDE/DDT	Obese adults undergoing bariatric surgery in Portugal. Background exposure.	Adipose methoxychlor associated with LDL. Adipose methoxychlor and HCH lindane associated with Framingham CVD risk score.	(317)
	PCBs, DDE	Obese adults without diabetes.	Adipose PCBs and DDE associated with weight, BMI, WC, and CT-VAT. Adipose PCBs and DDE associated with visceral adipose and visceral/ subcutaneous ratio.	(107)
	HCH, endosulfans, Aldrin, dieldrin, DDT, DDE	Adults with and without MetS. Background exposure.	β-HCH and Aldrin associated with MetS.	(391)
	PCB, OC pesticides, dioxin, HCB, DDE, BDE	PIVUS older adults, background exposure. Cross-sectional and prospective	Cross sectional: Trans- nonachlor positively associated with WC in males, no association in females. DDE positively associated with WC in males and females. HCB positively associated with WC in males but not in females. OCDD not associated with WC in males or females. PCB associations were positive, negative, or null based on congener and gender. Prospective: trans- nonachlor not associated with WC. OCDD associated with WC in females but not in males. DDE associated with WC in males but not in females. PCB associations were positive, negative, or null based on congener and gender.	(226)
	PCBs, OC pesticides	PIVUS older adults, background exposure.	Sum of OC pesticides and of less-chlorinated PCBs were positively associated with weight gain. Sum of highly- chlorinated PCBs were negatively associated with weight gain.	(241)
	PCBs	Non-obese adults in the Seguimiento Universidad de Navarra (SUN) Project	PCBs associated with increased risk of becoming obese.	(108)
	PCBs, DDE, β-HCH	Obese and normal weight individuals in Belgium. Case-control. Background exposure.	β-HCH positively associated and NDL PCBs negatively associated with BMI, WC, fat mass percentage, and	(106)

Class	Compound(s) Studied	Population	Finding	Reference
			total adipose tissue. DDE not associated.	
	Dioxin, oxychlordane, trans-nonachlor, DDT	NHANES 1999- 2002 adults. Cross-sectional. Background exposure.	DDT positively associated with WC in females but negatively associated in males. OC pesticides positively associated with BMI in males and negatively associated in females.	(110)
	NDL PCB, DL PCB, HCB, DDE	Flemish adults. Background.	In men and women, NDL PCB negatively associated with BMI and HCB positively associated with BMI. Also in women, DDE and DL PCB positively associated with BMI.	(104)
	PCBs, dioxin, BDE, DDE, OC pesticides	PIVUS older adults, background exposure.	OCDD, PCBS 74, 99, 105, 118, HCB, and DDE positively associated with fat mass. PCBs 156, 157, 169, 170, 180, 189, 194, 206, and 209 negatively associated with fat mass.	(332)
	PCBs, DDE, HCB	Adults in highly polluted Eastern Slovakia.	PCBs, DDE, HCB associated with BMI.	(218)
	PCBs, DDE, HCB, OC pesticides	PIVUS older adults, background exposure.	Less chlorinated PCBs (105, 118), DDE, HCB, trans-nonachlor were positively related to visceral and subcutaneous adipose tissue (vAT and scAT). More highly chlorinated PCBs were negatively associated with vAT and scAT. PCB 189 had inverted U-shaped association with vAT/scAT.	
	PCBs, DDE, HCB, β-HCH, trans-nonachlor, oxychlordane	Cross-sectional study of Swedish women. Background exposure.	Some DL PCB congeners (PCB-105, PCB-118), DDE, HCB, and β-HCH positively associated with BMI. NDL PCBs (PCB-156 and PCB-180) negatively associated with BMI. OC pesticides not associated.	(128)
	PCBs, β-HCH, DDT, DDE, HCB, OC pesticides	Canadian males. Cross-sectional. Background exposure.	Total organochlorines not associated with BMI. β-HCH, DDE, and oxychlordane positively associated with BMI. PCBs, HCB, mirex, trans-nonachlor, and oxychlordane not associated with BMI.	(164)
	PCBs, β-HCH, DDT, DDE, HCB, OC pesticides	Canadian males. Cross-sectional. Background exposure.	Total organochlorines, NDL PCBs, DDE, HCB, β-HCH, trans-nonachlor, oxychlordane positively associated with BMI. DDT and mirex not associated with BMI.	(312)
	DDE	African American women in U.S. Cross-sectional. Background exposure.	DDE positively associated with BMI but not waist-hip ratio.	(343)
Polybrominated flame retardants (BFRs)	PBBs and PBDEs	NHANES 2003- 2004 adults. Background exposure.	PBB-153 nonlinearly associated with MetS and WC. PBDE-153 inverted U shaped associated with MetS.	(239)
	PBDEs	PIN study pregnant women in US. Background exposure.	Milk levels PBDEs associated with BMI in female moms.	(91)
Polycyclic Aromatic Hydrocarbons (PAHs)	PAH metabolites	NHANES 2001- 2008 adults. Background exposure.	Urinary 2-phenanthrene positively associated with obesity. 1− naphthalene negatively associated with obesity. 2-naphthalene, 1− phenanthrene and 2− phenanthrene positively associated with 3+ risk factors for MetS.	(324)
Phthalate Esters	Phthalates	NHANES 2003- 2008	High MW metabolites (MECPP, MEHHP, MEOHP, MEHP, MBzP, MCNP, and MCOP) associated with obesity in male and female adults.	(59)

Class	Compound(s) Studied	Population	Finding	Reference
			DEHP metabolites associated with obesity in female adults. DEHP and high MW metabolites associated with obesity in males 60+ yrs old.	
	Phthalates	NHANES 1999- 2002. Background exposure.	MEP associated with BMI in adult males and females. MBP inversely associated with BMI and WC in elderly, non- significant positive trend in males but inverse in females. MBzP positively associated with BMI and WC in adult males, not associated in females. MEHP inversely related to BMI and WC in adult females. MEHHP associated with adult males, not associated in females.	(145)
	Phthalates	NHANES 1999-2002 male adults	MBzP, MEHHP, MEOHP, and MEP associated with WC.	(370)
Bisphenol A (BPA) and Bisphenol A diglycidyl ether (BADGE)	BPA	In CHIANTI Italian adults	BPA associated with WC and weight	(122)
	BPA	NHANES 2003-2006 adults.	BPA associated with general and abdominal obesity.	(65)
	BPA	Cross-sectional study in Chinese adults.	BPA associated with general and abdominal obesity.	(420)
	BPA	NHANES 2003- 2004 adults.	BPA not associated with BMI.	(216)

Table 9

POP Exposures and Associations with Diabetes

Class	Compound(s) Studied	Population	Finding	Reference
Organochlorines	OC pesticides, PCBS, PBB	CARDIA young adults without diabetes, age 27.2+/−3.3yrs old, BMI 29.1+/− 6.7 kg/m2. Background exposure.	p,p'-DDE and PCBs predicted HOMA-IR.	(230)
	PCDDs, PCDFs, dioxin-like PCBs, non- dioxin-like PCBs, OC pesticides	NHANES 1999-2002. Adults without diabetes. Background exposure.	Oxychlordane, trans-nonachlor, PCB170, PCB187 strongly associated with higher HOMA-IR.	(222)
	PCDDs, PCDFs, dioxin-like PCBs, non- dioxin-like PCBs, OC pesticides	NHANES 1999-2002. Adults without diabetes. Background exposure.	OC pesticides and PCBs associated with high fasting glucose	(223)
	PCB, OC pesticides, DDE, Dioxins	NHANES 1999-2002. Adults with background exposure.	PCB-153, trans-nonachlor, oxychlordane, DDE, OCDD and PCDD 73 strongly associated with T2D prevalence. TCDD unrelated to diabetes prevalence.	(224)
	PCB, OC pesticides, dioxin, HCB, DDE, BDE	Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS). Older adults, background exposure. Cross-sectional and prospective	PCBs, sum of OC pesticides, and trans-nonachlor associated with incident T2D. Dioxin not associated with incident diabetes.	(227)
	PCB, PCDD, PCDF, OC pesticides	NHANES 1999-2002 Adults with background exposure.	Dioxin-like PCBs and OC pesticides associated with diabetes. PCDDs and non-dioxin-like PCBs were not associated with diabetes. PCDFs were weakly associated with diabetes.	(225).
	PCB, HxCDD, DDT	NHANES 1999-2002. Adults with background exposure.	Serum 1, 2, 3, 4, 6, 7, 8-PCDD, PCB 126, DDT levels associated with diabetes.	(114)
	OC pesticides, DDE, DTT	HHANES 1982-1984: Mexican-American Adults with background exposure.	Serum trans-nonachlor, β-hexachlorocyclohexane, oxychlordane, and highest exposure to DDT and DDE associated diabetes. Trans-nonachlor and β- hexachlorocyclohexane associated with elevated serum glucose.	(85)
	PCB, DDE, OC pesticides, HCB	Mohawk Nation at Akwesasne adults	Serum PCB, DDE, HCB associated with diabetes. Mirex negatively associated with diabetes.	(80)
	PCB, DDE,	Great Lakes Consortium for the	DDE and dioxin-like mono-ortho	(398)
	PBDE, BDE	Health Assessment of Great Lakes Sport Fish Consumption adults.	PCBs associated with diabetes. Non-dioxin like PCBs and PBDEs were not associated with diabetes.	
	OC pesticides, PCBs, PDBE, PBB	CARDIA(Coronary Artery Risk Development in Young Adults) 18- 30yrs old in US without diabetes. Prospective study, background exposure.	Low dose trans-nonachlor, oxychlordane, mirex, highly chlorinated PCBs, and PBB 153 associated with increased risk diabetes incidence.	(229)

Class	Compound(s) Studied	Population	Finding	Reference
	PCBs, DDE	Obese adults without diabetes. Background exposure.	Serum PCBs associated with fasting glucose and abnormal GTT, while negatively associated with HOMA-B. Serum PCB180 negative associated with fasting insulin. Adipose PCBs associated with HbA1C and fasting glucose. Serum and adipose DDE associated with glucose levels during GTT and abnormal GTT.	(107)
	HCH, HCB, OC pesticides, TCDD, DDE/DDT	Obese adults undergoing bariatric surgery in Portugal. Background exposure.	Adipose total POPs associated with HOMA-IR and dysglycemia. Adipose methoxychlor associated with glycemia, HbA1c. Adipose DDE associated with glucose metabolism and HbA1c.	(317)
	PCB, DDT, DDE, HCB	Nurse's Health Study: female adults in US. Background exposure. Prospective study	Plasma HCB positively associated with incident T2D. PCBs not significantly associated with increased T2D risk.	(429)
	Oxychlordane, trans-nonachlor, p,p'-DDE, PCB 153, BDE 153	Adults in Finland. Background exposure.	Oxychlordane, trans-nonachlor, p-p'-DDE, and PCB 153 positively associated with prevalent T2D.	(24)
	PCB, DDE	Elderly adults in Faroese Islands. Background exposure	Elderly adults with T2D had higher PCB levels. In nondiabetics, increased PCB levels associated with increased fasting glucose and decreased fasting insulin.	(132)
	PCBs, PCDDs, PCDFs	Healthy adults in Japan. Background exposure.	Accumulated toxic equivalents (TEQs) of PCDDs, PCDFs, dioxin-like PCBs, and total dioxins associated with HbA1c.	(400)
	HCB, DDE	Swedish fishermen and their wives.	PCB-153 and p,p'-DDE associated with diabetes prevalence.	(337)
	High levels of exposure			
	TCDD	Healthy adults without diabetes around Superfund site in Arkansas	TCDD associated with higher plasma insulin at fasting and 30, 60, and 120 min during GTT	(86)
	PCBs, DDE, OC pesticides	Anniston Community Health Survey adults near PCB-contaminated area.	PCB associated with diabetes. When sex-stratified, PCBs had a positive association in women and an inverse association in men. DDE associated with diabetes prevalence in women.	(357)
	PCB, PBB	Michigan PBB cohort exposed to contaminated food, prospective study.	PCB associated with increased incidence of diabetes in women.	(411)
	PCBs, DDE, HCB	Adults in highly polluted Eastern Slovakia.	Circulating PCBs, DDE, HCB correlated with fasting glucose and seruminsulin.	(218)
	OC pesticides	Agricultural Health Study: pesticide applicators and spouses in US without diabetes. Occupational exposure	Having ever used and cumulative use of aldrin, chlordane, and heptachlor increased odds of diabetes incidence.	(276)
	PCB, DDE, DDT, HCB, β-HCH	PCBRISK cross- sectional survey of heavily polluted area of Eastern Slovakia	PCBs, DDE, DDT, HCB, and β-HCH associated with prediabetes, but only PCB, DDT, and DDE associated with diabetes.	(401)
	TCDD	US Air Force veterans of Operation Ranch Hand (Air	Agent Orange associated with higher risk of glucose abnormalities and T2D.	(150)

Class	Compound(s) Studied	Population	Finding	Reference
		Force Health Study) from Vietnam War 1961-1971. Occupational exposure		
	TCDD	US Air Force veterans of Operation Ranch Hand (Air Force Health Study) from Vietnam War 1961-1971. Occupational exposure.	Dose-response relationship between TCDD-contaminated Agent Orange and T2D in veterans with background levels of exposure.	(247)
	TCDD	Residents surrounding Seveso, Italy, industrial accident.	Residents living in medium-exposure areas to TCDD had higher T2D mortality as compared to high-exposure areas.	(43)
		Maternal/PrenatalExposure		
	PCB and DDE	Swedish mothers and their children. Background exposure.	Nonsignificant trend of maternal exposure to PCB-135 or DDE and decreased T1D development in the offspring.	(326)
	PCBs	Collaborative Perinatal Project (CPP): mothers with and without diabetes and their children	Maternal exposure to PCBs monotonically associated with T1D in offspring.	(246)
	DDE, PCB, HCB, HCH, Organophospha te pesticides	PELAGIE cohort of pregnant women in Brittany	Prenatal exposure to DDE was associated with a decrease in insulin in girls but not boys. Prenatal exposure PCB153 was associated with decreased insulin.	(100)
	PCBs, DDE, HCB	Adults frompolluted area of Slovakia whose mothers experienced high level s of exposure.	Maternal exposure to PCBs associated with impaired fasting glucose.	(217)
Polybrominated flame retardants (BFRs)	PBBs and PBDEs	NHANES 2003-2004, adults, BMI 28.3+/- 5.9kg/m2	PBB-153 and PBDE-153 positively associated with prevalent diabetes. PBB-153 associated with glycemia. PBDE-99 and PBDE-100 nonsignificant positive association with diabetes. PBDE-28 and -47 not associated with diabetes.	(239)
	PCB, DDE, PBDE, BDE	Great Lakes Consortium for the Health Assessment of Great Lakes Sport Fish Consumption adults.	PBDEs not associated with diabetes.	(398)
	OC pesticides, PCBs, PDBE, PBB	CARDIA(Coronary Artery Risk Development in Young Adults) 18-30y olds in US without diabetes. Prospective study, background exposure.	Low dose PBB153 associated with increased risk of diabetes incidence.	(229)
	PCB, OC pesticides, dioxin, HCB, DDE, BDE	Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS). Older adults, background exposure. Cross-sectional and prospective	BDE not associated with T2D prevalence or risk of T2D incidence.	(227)
	PCB, PBB	Michigan PBB cohort exposed to contaminated food, prospective study.	PBB not a risk factor for diabetes incidence.	(411)
	Oxychlordane, trans-nonachlor, p,p'-DDE, PCB 153, BDE 47, BDE 153	Adults in Finland. Background exposure.	BDE 47 and BDE 153 not associated with T2D.	(24)

Class	Compound(s) Studied	Population	Finding	Reference
Polycyclic Aromatic Hydrocarbons (PAHs)	PAHs	NHANES merged 2001-2006. Adults, background exposure.	Urinary PAH biomarkers positively associated with diabetes. 0	(28)
	PAHs	Chinese adults, background exposure.	Urinary PAH metabolites had dose-response association to increased risk of diabetes.	(432)
	8 PAH metabolites	NHANES 2001-2008 adults. Background exposure.	1-naphthalene, 2-naphthalene, 2-phenanthrene and 1-pyrene associated with T2D.	(324)
Phthalate Esters	BPA and phthalate metabolites	Nurses' Health Study (NHS) and NHSII female adults. Background exposure.	In NHSII- urine butyl phthalates (MBP and MiBP) and total phthalate metabolites positively associated with incident T2D. In older NHS cohort, no significant association between phthalates and incident T2D.	(376)
	Phthalates	NHANES 2001-2008 adults without diabetes. Background exposure.	Urinary MnBP, MiBP, MCPP, and DEHP (sum of MEHP, MEHHP, MEOHP) positively associated with fasting blood glucose, fasting insulin, and HOMA-IR	(163)
	Phthalates	ElderlyKorean adults.	Sum of DEHP metabolites (sum of MEHHP and MEOHP) associated with HOMA. No association between MnBP and HOMA.	(199)
	Phthalates and BPA	NHANES 2003-2008 adolescents (12-19yrs old). Background exposure.	DEHP metabolites (MEHP, MECPP, MEHHP, and MEOHP) associated with HOMA-IR and insulin resistance. Lower molecular weight phthalates (MEP, MBP, MiBP, MBP) (found in cosmetics and personal use items) not associated with HOMA- IR or insulin resistance.	(395)
	Phthalates	Healthy Mexican women. Background exposure.	Higher levels of DEHP, MEHHP, MEOHP, and MECPP are positively associated with diabetes. MBzP negatively associated with diabetes.	(378)
	Phthalates	NHANES 1999-2002	MBP, MBzP, and MEP associated with increased HOMA, but only MBzP and MEP remained significant after adjustment for renal and hepatic function.	(370)
Bisphenol A and Bisphenol A diglycidyl ether (BADGE)	BPA	National Health Examination Survey of Thai adults. Background exposure.	Serum BPA positively associated with diabetes and impaired fasting glucose.	(20)
	BPA	Adults in Iran. Background exposure.	Urine BPA positively associated with diabetes prevalence and HbA1c.	(23)
	BPA	Adults in Korea. Background exposure.	Urine BPA not significantly associated with T2D.	(201)
	BPA	NHANES 2003-2008 adults. Background exposure.	Urine BPA positively associated with diabetes.	(349)
	BPA and phthalate metabolites	Nurses' Health Study (NHS) and NHSII female adults. Background exposure.	In NHSII- urine BPA positively associated with incident T2D. In older NHS cohort, no significant associations between BPA and incident T2D.	(376)

Class	Compound(s) Studied	Population	Finding	Reference
	BPA	NHANES 2003-2004 adults.	BPA associated with diabetes (adjusted for BMI, WC).	(216)
	BPA	NHANES 2005-2006 adults.	BPA associated with diabetes, but association lost in fully adjusted models (age, sex, race, education, income, smoking, BMI, WC, urinary creatinine).	(263)

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